Tobacco Addiction: Implications for Treatment and Cancer Prevention

Paul M. Cinciripini, Stephen S. Hecht, Jack E. Henningfield, Marc W. Manley, Barnett S. Kramer*

The American Society of Clinical Oncology and the National Cancer Institute convened a symposium in June 1996 on tobacco addiction. Additional support for the symposium was provided by the American Medical Women’s Association and the American Society of Preventive Oncology. The goals of this conference were to describe the burden and public health consequences of tobacco addiction, to describe the state of science for the treatment of nicotine dependence, and to explore new strategies to increase quit rates and to prevent the uptake of tobacco use. This article summarizes and integrates the meeting presentations on tobacco addiction and includes the topics of smoking prevalence; psychobiologic aspects of nicotine dependence; and implications for disease, treatment, and prevention. Comments on regulatory approaches and national strategies for reducing dependence are also summarized in presentations by Dr. David Kessler, former Food and Drug Administration Commissioner, and Dr. C. Everett Koop, former U.S. Surgeon General. [J Natl Cancer Inst 1997;89:1852–67]

“Tobacco drieth the brain, dimmeth the sight, vitiateth the smell, hurtest the stomach, destroyeth the concoction, disturbeth the humors and spirits, corrupteth the breath, induceth a trembling of the limbs, exicateth the windpipe, lungs, and liver, annoyeth the milt, scorchteth the heart, and causeth the blood to be adjusted.”

Tobias Verner, 1577–1660

Introduction

Organization of the ASCO/NCI Conference on Tobacco Addiction (1)

More than 300 years after Tobias Verner made the above observations, most were officially confirmed in a report to the U.S. Surgeon General on the health consequences of smoking (2). By then, our nation was in the midst of the current epidemic of tobacco-related disease. The ensuing 3 decades of experience since the original Surgeon General’s report on tobacco smoking have brought additional sobering insights. First, adverse health consequences extend to noninhaled forms of tobacco (3). Second, simple provision of information about the consequences of tobacco use to the public is insufficient to end the epidemic. Less than 3% of smokers become nonsmokers each year (4). Third, tobacco use is not simply a habit, but an addiction. Less than 15% of Americans who quit smoking for a day remain abstinent 1 year later (4,5). Finally, and tragically, with its inception in early adolescence, tobacco addiction is a pediatric disease, not simply an affliction of adulthood. The median age of initiation to tobacco use is below 15 years in many countries (6).

The treatment of nicotine dependence may require the same type of behavioral, societal, and pharmacologic strategies extended to the management of other abused substances, such as alcohol, cocaine, and heroin. With this in mind, the American Society of Clinical Oncology (ASCO) and the National Cancer Institute (NCI) convened a symposium in June 1996 on tobacco addiction. Additional support for the symposium was provided by the American Medical Women’s Association and the American Society of Preventive Oncology. In keeping with ASCO’s published position statement on tobacco control (7), the goals of this conference were to describe the burden and public health consequences of tobacco addiction, to describe the state of science for the treatment of nicotine dependence, and to explore new strategies to increase quit rates and to prevent the uptake of tobacco use. This article cannot review all aspects of nicotine dependence, but it will summarize and integrate the meeting presentations on tobacco addiction and include the topics of smoking prevalence; biologic aspects of nicotine dependence; and implications for disease, treatment, and prevention. Regulatory approaches and national strategies for reducing dependence are also summarized in presentations by Dr. David Kessler, former Food and Drug Administration (FDA) Commissioner, and Dr. C. Everett Koop, former U.S. Surgeon General.

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The presentations of each conference participant are referenced at the beginning of the section in which the material is discussed (see Appendix Table 1 for a list of the participants and their institutions).

**The Epidemic of Tobacco Use (8)**

The former Surgeon General has stated that cigarette smoking is the chief avoidable cause of death in our society, and many believe that it represents the most important public health issue of our time. In the United States, there are an estimated 434,000 deaths per year from tobacco use, equating to about 1200 per day or about 50 per hour. Tobacco is responsible for the yearly deaths of more Americans than alcohol, cocaine, heroin, homicide, suicide, car accidents, fires, and acquired immunodeficiency syndrome combined (9).

Approximately one quarter of the U.S. adult population (about 48 million people) currently smoke (10,11). Approximately one fifth of U.S. high school seniors smoke daily. The rate is much greater among school dropouts. After a decline through the late 1970s and early 1980s (10), followed by roughly stable rates, current smoking among high school students increased from 27.5% in 1991 to 30.5% in 1993 to 34.8% in 1995 (12,13). Thus, adult smokers who quit or die are being replaced by children who smoke.

There have also been sharp increases in the past 2 decades in the use of smokeless tobacco, occurring almost exclusively among males between the ages of 18 and 34 years (10). For example, from 1970 through 1991, the percentage of males under age 25 years who reported using either chewing tobacco or moist snuff rose from 2.2% to 8.4%. During the same period, cigarette smoking for this group declined from 38% to 22.9%. More than 5 million users of moist snuff are reported in the United States alone (14).

In recent decades, U.S. rates of lung cancer have increased among both men and women, and, in the late 1980s, lung cancer surpassed breast cancer as the most common cancer killer of women. Recently, a decline has been observed in age-adjusted mortality from lung cancer among men, consistent with their reduction in smoking (15). Unfortunately, this decline has not yet been observed among women, for whom the increase in lung cancer mortality continues. This pattern is consistent with the fact that the rise in women’s smoking occurred subsequent to that in men. It is estimated that 43,900 and 66,000 women will die of breast and lung cancer, respectively, in 1997 (15).

The impact of smoking is a growing worldwide problem. Peto et al. (16,17) estimated that, in developed countries in 1995, there would be about 2 million deaths attributable to smoking—1.5 million men and 0.5 million women. In the former socialist economies of Eastern Europe, serious increases in smoking-attributed deaths are occurring, particularly among men. Rates for women are steadily increasing, but at a lower rate than for men; however, these rates are expected to increase as tobacco marketing efforts focus on these women.

Reliable data are more difficult to obtain from some of the developing countries. The general pattern reported is a high prevalence of smoking among men (for example, >60% in Bangladesh and India) but much lower use among women (excepting Nepal, which has high rates among both men and women). A similar pattern is seen in the Pacific Region, including China, where estimates in the 1980s showed more than 60% of men but less than 10% of women smoking (18). The concern is that tobacco marketing will target the women in these populations.

Peto et al. have estimated that global tobacco-related deaths will exceed 3 million per year in the 1990s. In 30–40 years, global tobacco-related deaths could exceed 10 million annually (19). The World Health Organization projects that, unless something is done, one in 10 people now alive will die of a tobacco-related disease.

**Benefits of Quitting**

The benefits of cessation and their impact on the public health are substantial. Compared with nonsmokers, smokers exhibit a dose-dependent increase in the risk of dying from lung (20), pancreatic (21), head and neck, and renal (22) cancers, as well as a twofold increase in risk of developing bladder cancer (23) and leukemia (24) and a threefold increase in risk of myeloma (24). Moreover, it is clear that former smokers live longer than continuing smokers and that the benefits of quitting extend into the later age groups. In comparison with continuing smokers, people who quit smoking before age 50 years show a 50% reduction in risk for all causes of death in the subsequent 16 years, and, by age 64 years, their risk of mortality is similar to that of never smokers of the same age (9). As shown in Table 1, factors such as health status at the time of quitting, duration of abstinence, and previous level of tobacco exposure determine the magnitude of risk reduction achieved. For example, relative to nonsmokers, the mortality ratio for males with no concurrent illness who smoked more than 21 cigarettes per day averaged 2.73 for current smokers and 1.77 for former smokers with 6–10 years of abstinence. In the case of cancer mortality, the change in rates may also vary by site. For example, a 30%–50% reduction in lung cancer mortality risk has been noted for both sexes and for all histologic types after 10 years of nonsmoking; whereas, for cancer of the bladder or kidney, the risk to former smokers may be reduced by 50% within a few years following smoking cessation. A 50% reduction in risk for cancer of the oral cavity and esophagus has been observed as soon as 5 years after cessation (9).

**Implications for Disease and Prevention**

**Tobacco Use and Carcinogens (25)**

Nicotine dependence provides the link through which smokers are repeatedly exposed to carcinogenic and genotoxic elements associated with tobacco consumption. In the case of lung cancer, smokers are exposed in dose-dependent fashion to the major carcinogens underlying the disease, as shown in Table 2. These carcinogenic compounds are the polynuclear aromatic hydrocarbons (PAHs), typified by the classical carcinogen benz[a]pyrene (BaP), and the nicotine-derivated tobacco-specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butane (NNK). PAH and NNK are powerful pulmonary carcinogens in rodents, inducing tumors at total doses similar to those encountered in a lifetime of smoking (26,27). The metabolic activation and detoxification pathways for PAH and NNK are well understood and are the same in rodents and humans, although there are quantitative differences (28,29). The DNA adducts that are formed from PAH and NNK have been well characterized, and...
their role as major factors in the carcinogenic process has been established (30, 31). These same DNA adducts are found in the lungs of smokers (30, 31), and the role of specific adducts in causing permanent mutations has been elucidated (32). The bulky adducts resulting from the metabolic activation of BaP and NNK cause G to T mutations, while the methyl adducts formed from NNK produce G to A mutations. These mutations have been detected in K-ras oncogenes and p53 tumor suppressor genes isolated from lung tumors in smokers, and a dose-response relationship has been noted between G to T mutations in p53 and cigarette smoke exposure (33, 34).

As shown in Fig. 1, dependence on nicotine is a prerequisite to the multistage process of lung carcinogenesis, in which these mutations play a critical role (35). Moreover, in addition to their role in lung cancer, the nitrosamines are also considered major causative factors for cancers of the esophagus and pancreas. Both PAH and nitrosamines have been causally related to oral cancer, and aromatic amines have been associated with bladder cancer in smokers (26, 36).

Virtually all known carcinogens in tobacco products require metabolic activation for binding to DNA. There are competing detoxification reactions. The balance between metabolic activation and detoxification in an individual will, in part, determine that person’s risk for cancer upon carcinogen exposure. This balance is in large measure determined by individual levels and activities of carcinogen metabolizing enzymes, such as cytochromes P450, glutathione S-transferases, N-acetyltransferases, and uridine diphosphoglucuronosyl transferases (37).

Table 1. Overall mortality ratios among current smokers and former smokers, relative to never smokers, according to sex, duration of abstinence, and cigarette intake*

<table>
<thead>
<tr>
<th>Duration of abstinence, y</th>
<th>0 (current smokers)</th>
<th>&lt;1</th>
<th>1–2</th>
<th>3–5</th>
<th>6–10</th>
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<tr>
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<td></td>
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<td></td>
</tr>
<tr>
<td>1–20 cigarettes/day</td>
<td>2.22</td>
<td>2.49</td>
<td>2.38</td>
<td>2.03</td>
<td>1.63</td>
<td>1.38</td>
<td>1.06</td>
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<tr>
<td>≥21 cigarettes/day</td>
<td>2.43</td>
<td>2.77</td>
<td>2.64</td>
<td>2.25</td>
<td>2.04</td>
<td>1.77</td>
<td>1.27</td>
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<td>Females</td>
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<tr>
<td>1–19 cigarettes/day</td>
<td>1.60</td>
<td>1.58</td>
<td>1.96</td>
<td>1.41</td>
<td>1.14</td>
<td>1.10</td>
<td>1.01</td>
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<tr>
<td>≥20 cigarettes/day</td>
<td>2.10</td>
<td>3.39</td>
<td>2.58</td>
<td>2.03</td>
<td>1.60</td>
<td>1.38</td>
<td>1.15</td>
</tr>
<tr>
<td>Smokers with no current illness†</td>
<td></td>
<td></td>
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<tr>
<td>1–20 cigarettes/day</td>
<td>2.34</td>
<td>2.06</td>
<td>2.05</td>
<td>1.89</td>
<td>1.48</td>
<td>1.29</td>
<td>1.01</td>
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<tr>
<td>≥21 cigarettes/day</td>
<td>2.73</td>
<td>1.85</td>
<td>2.15</td>
<td>1.90</td>
<td>1.77</td>
<td>1.65</td>
<td>1.19</td>
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<tr>
<td>1–19 cigarettes/day</td>
<td>1.82</td>
<td>1.76</td>
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<td>1.42</td>
<td>1.01</td>
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<td>1.00</td>
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<tr>
<td>≥20 cigarettes/day</td>
<td>2.46</td>
<td>3.33</td>
<td>2.15</td>
<td>1.44</td>
<td>1.46</td>
<td>1.18</td>
<td>0.95</td>
</tr>
</tbody>
</table>

†Former smokers with heart disease, cancer, stroke, or other serious illness at the time of enrollment in the study were excluded.

Table 2. Smoking and lung cancer: Causative agents*

<table>
<thead>
<tr>
<th>Carcinogens</th>
<th>Modifying agents</th>
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<tbody>
<tr>
<td>Strong evidence†</td>
<td>Co-carcinogens (catechols)</td>
</tr>
<tr>
<td>NNK‡</td>
<td>Tumor promoters (phenols and others)</td>
</tr>
<tr>
<td>PAH§ (benz(a)pyrene, benzo(b), and j]fluoranthenes, 5-methylchrysene, dibenz[a]anthracene, and Indeno[1,2,3-cd]pyrene)</td>
<td>Toxic aldehydes (acrolein)</td>
</tr>
<tr>
<td>Weak evidence</td>
<td>Oxidative damage and free radicals</td>
</tr>
<tr>
<td>²¹⁰Po, Cr, Cd, and Ni</td>
<td>Aldehydes</td>
</tr>
</tbody>
</table>

‡Nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone.
§Polynuclear aromatic hydrocarbons.

Fig. 1. Scheme linking nicotine addiction to lung cancer through the major pulmonary carcinogens of tobacco smoke—polynuclear aromatic hydrocarbons (PAH) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK).
specific carcinogen adducts to DNA or protein provides one way of distinguishing individuals with differing risks of cancer. For example, the higher risk of lung cancer in African-American smokers than in Caucasian smokers may be related to poorer detoxification of NNK (38). Another example is found in the higher levels of 4-aminobiphenyl hemoglobin adducts in smokers with a higher risk of bladder cancer. Adduct levels are controlled in part by dose and by one’s ability to activate the carcinogen via cytochrome P450 1A2 or to detoxify it by N-acetylation (39).

**Smokeless Tobacco (40)**

Smokeless tobacco users are also exposed to high concentrations of nicotine cancerigenic nitrosamines. The three leading brands of moist snuff in the United States, Copenhagen, Skoal, and Kodiak, contain substantial amounts of nicotine (i.e., 10.9–11.9 mg/g tobacco). Importantly, 22%–60% of this nicotine is in the unprotonated form because of the relatively high pH (3). Unprotonated nicotine is rapidly absorbed through the oral mucosa (41). By contrast, products with a lower market share, such as Hawken and Skoal, have significantly lower amounts of available nicotine (3).

Carcinogenic nitrosamines are formed from nicotine and other tobacco alkaloids during the manufacturing of moist snuff products (3). The two most carcinogenic nitrosamines in tobacco products are N’-nitrosornicotine (NNN) and NNK. They are present in average amounts of 7.7 and 1.2 μg/g tobacco, respectively, and their structures are shown in Fig. 2.

The levels of NNN and NNK are far higher than those of carcinogens in any other consumer product (42). Moreover, concentrations of NNN and NNK in U.S. moist snuff products have not substantially changed over the past 20 years (43). A bioassay of these two compounds applied to the oral cavity of the rat demonstrated a substantial and statistically significant incidence of oral tumors (44). A recent study (45) has also demonstrated an association between NNK metabolites in the urine of snuff-dippers and the presence of oral leukoplakia.

**Tobacco Use and Chemoprevention (25)**

Cessation of all tobacco use is clearly the best way to prevent tobacco-related cancers, but recent studies suggest that chemoprevention may be a way to partially counteract carcinogen exposure associated with continued use of tobacco. This approach may be particularly important for the heavily nicotine-dependent smoker, whose successful long-term abstinence may require multiple cessation attempts and/or intensive treatment efforts before it can be achieved. For example, a near lifetime administration of phenethyl isothiocyanate (PEITC), which occurs naturally as a conjugate in watercress and other cruciferous vegetables, has been shown to inhibit lung cancer induction in rats treated with NNK (46,47). PEITC selectively inhibits the metabolic activation of NNK in the rat lung (48,49) and in humans exposed to PEITC through watercress consumption (50). A large number of naturally occurring compounds are available that are able to inhibit lung tumor development caused by NNK or BaP (46) that could be employed for the chemoprevention of lung cancer in smokers. Some compounds, such as myo-inositol, can also inhibit lung cancer in animals when administered after carcinogen exposure and could potentially be useful for the chemoprevention of lung cancer in ex-smokers (51). However, the inverse relationship recently observed between lung cancer incidence and β-carotene supplementation among smokers (52,53) indicates that caution should be exercised in this high-risk group. The potential application of chemoprevention strategies has been discussed elsewhere (54), and, although chemopreventive agents hold promise, more research is needed to determine whether they are effective at reducing the cancer risk of smokers.

**Tobacco Use and Molecular Epidemiologic Approaches to Risk Identification (55)**

The risk assessment process is often multidisciplinary and complex because of interindividual variation in susceptibility to cancer. Understanding this process can allow us to identify smokers with the highest risks of developing cancer, perhaps targeting them for intensive smoking cessation interventions, chemoprevention trials, or tailored educational messages. Molecular epidemiology provides a means for studying the multistep processes that occur between exposure and cancer, and results from these investigations highlight the role of genetic susceptibility in carcinogenesis.

Cigarette smoking is the major determinant of lung cancer; yet, fewer than 20% of lifetime cigarette smokers will develop lung cancer. The risk of lung cancer depends on the dose of tobacco, the duration of smoking, the types of tobacco, the type of cigarette, and host susceptibility. Sometimes, gene–environment interactions are suggested even by natural subgroups within the population. For example, it has been reported (56) that the odds ratios for major lung cancer types were consistently higher for women than for men at every level of exposure to cigarette smoke. Furthermore, this sex difference could not be explained by differences in baseline exposure, smoking history, or body size, suggesting that it was the result of higher susceptibility to tobacco carcinogens among women. Genetic factors may influence carcinogen absorption, distribution, or accumulation in target tissue and thereby modulate the internal levels of exposure [e.g., genetic polymorphisms in the enzymes responsible for activation {cytochrome P450s} and detoxification {glutathione S-transferase enzymes (57)}] of tobacco carcinogens.

Another determinant of susceptibility to carcinogens may be mutagen sensitivity, which can be measured in an in vitro assay of mutagen-induced chromatid breaks in cultured lymphocytes. Individuals with large numbers of breaks are considered to be at higher risk of developing cancer because of a decreased ability to repair induced damage. Case-control studies (58–61) have indicated that bleomycin-induced mutagen sensitivity is an in-
dependent risk factor for head and neck and lung cancers. A meta-analysis of three case-control studies of heavy smokers (62) showed an odds ratio of 11.5 (95% confidence interval [CI] = 5.0–26.6) for cancers of the head and neck in the absence of the hypersensitive phenotype. However, among heavy smokers who exhibited mutagen hypersensitivity, the odds ratio was 44.6 (95% CI = 17.4–114). Similar interactions have been noted for lung cancer susceptibility. It is informative to compare never smokers and former smokers stratified on the basis of mutagen sensitivity. Compared with those who never smoked and who were not mutagen sensitive (the reference group), those who never smoked but were mutagen sensitive had a twofold elevated risk. Former smokers who were not mutagen sensitive were still at increased risk (about threefold). Thus, exposure to sufficient levels of tobacco smoke can overwhelm whatever nonsusceptible genotype or phenotype one has. Finally, for those who were mutagen sensitive and who smoked, the risk was much higher, indicating an interaction between mutagen sensitivity and smoking.

Another example is a restriction fragment length polymorphism in codon 72 of the p53 gene, which has been implicated in lung cancer risk. Patients with the susceptible genotype (coding for Proline/Proline) appeared to have an earlier age at diagnosis and lower mean cigarette pack-years of exposure than did patients with the Arginine/Arginine- or the Arginine/Proline-coding genotypes (63). These and other results suggest that individuals with a susceptible genotype tend to develop cancer at earlier ages and with less cigarette exposure. It is interesting that there are considerable ethnic differences in the prevalence of the susceptible genotype, with estimates of 26% for whites, 20% for African-Americans, 10% for Japanese, and only 2.5% for Mexican-Americans; this observation may partly explain the latter group’s lower rates of lung cancer.

It is likely that there are numerous genotypic factors that together explain differences in risk. The metabolism of the many carcinogens in cigarette smoke is complex. Thus, multiple susceptibility factors must be accounted for to represent the true dimensions of gene–environment interactions and to construct the most appropriate quantitative risk-assessment models.

Psychobiological Aspects of Nicotine Dependence

Although the initiation of tobacco use may be dependent on social factors (e.g., peer use, parental approval, and poor school performance) and the marketing efforts of tobacco companies, biologic factors play a fundamental role in the development of nicotine dependence and pose significant barriers to achieving tobacco abstinence (64,65). Among those trying even a single cigarette, 33%–50% will become nicotine dependent (66). Among regular tobacco users, the incidence of dependence is even more substantial, ranging from 70% to 90% (67–69). In fact, the risk of developing dependence to tobacco is higher than that observed following initial use of cocaine or alcohol (67,68,70). The effects of nicotine involve subtle, diverse, and behaviorally relevant psychoactive properties, the development of pharmacologic tolerance, and a reduction in symptoms of withdrawal following nicotine administration. Understanding these factors may provide insight into the mechanisms responsible for the development of nicotine dependence and improve our approach to treatment.

Chemistry of Nicotine (71)

Nicotine is a water- and lipid-soluble base with a pKa of 8.0 (64,72). Thus, nicotine delivered in alkaline cigar and pipe smoke and smokeless tobacco is readily absorbed across mucosal membranes of the mouth and nose (64,72). Cigarette smoke is acidic and, for effective absorption, must be inhaled in the pulmonary alveoli, where absorption is rapid (72–74).

Cigarettes contain 6–11 mg of nicotine, of which the smoker can absorb 1–3 mg irrespective of tobacco company provided nicotine-yield ratings and which is sufficient to establish and sustain nicotine dependence (72,75). A typical pack per day cigarette smoker absorbs 20–40 mg of nicotine each day, achieving concentrations of 25–35 ng/mL of plasma by the afternoon (72). The plasma half-life of nicotine is approximately 2 hours, and the half-life of its primary metabolite, cotinine, is approximately 20 hours (76).

Psychophysiological Responses to Nicotine

Nicotine is rapidly distributed from the bloodstream, binding to various tissues and activating nicotinic cholinergic receptors or binding sites. Activation of these receptors leads to alteration of spontaneous electroencephalogram and evoked brain electrical potentials, alteration of local cerebral glucose metabolism, modulation of adrenal and pituitary hormones, an increased heart rate, and changes in skeletal muscle tension (72). The effects may also produce pleasure and satisfaction in humans and are sufficiently rewarding to lead animals as well as humans to press levers that lead to repeated injections of nicotine (64,72,77). In addition, evidence also suggests that nicotine may enhance vigilance, memory, and task performance, independent of withdrawal relief (78–81).

Nicotine’s diverse, yet subtle, psychoactive actions may be related to its simultaneous actions on many types of neurons and its effects on the release of dopamine, norepinephrine, and serotonin (5-hydroxytryptamine or 5-HT). These neurotransmitter systems may be modulated by nicotine’s direct or indirect effects on receptors or through its other cholinergically mediated actions (72). Nicotine’s effect on dopamine release (nucleus accumbens) and synthesis in the mesolimbic system may be important to the motivational and reinforcing properties of the drug (82,83). Dopamine release in the nucleus accumbens has been associated with self-administration of nicotine, opiates, and cocaine; brain electrical stimulation; anticipation of eating and sexual behavior; the effects of rewards or incentives (83); and avoidance of aversive stimuli (81). Nicotine may also increase turnover of norepinephrine in the hypothalamus and release in the locus coeruleus. This type of noradrenergic stimulation has been related to enhanced attention to significant stimuli and reduction in the salience of irrelevant stimuli (81). Moreover, nicotine may stimulate 5-HT release in the median raphe nuclei, where high-affinity nicotine binding sites exist, as well as serotonergic neurons in the hypothalamus and striatum (83). Such actions could have implications for understanding the relationship between smoking and depressed mood, given the favorable clinical response of patients with major depression treated with serotonin re-uptake inhibitors (84).

Recent studies (85) also suggest that an up-regulation (i.e., increased expression) of nicotine receptors may result with
chronic use, but many of these receptors are desensitized or inactive. Tolerance may develop as capacity to recruit new receptors to compensate for desensitization is outstripped by their rate of inactivation (86). In contrast, down-regulation (i.e., decreased expression) may take place when chronic use is terminated. This process has been referred to as metabolic tolerance, and its regulation may have a substantial genetic component (86).

Most, if not all, effects of nicotine on the central nervous system are dose dependent, and tolerance has been observed to differing degrees across many effects (64,72). Nicotine tolerance appears to be acquired substantially during youth as individuals progress from smoking a few cigarettes on initial exposure to higher levels of consumption (87,88). After a period of nicotine exposure assumed to be at least “several weeks” (89), physical dependence on nicotine may ensue. It has been suggested (86) that repeated exposure to nicotine produces tolerance in sensitive individuals, which in turn reduces the net effect of the drug. This leads to a compensatory increase in consumption to obtain the desired effect (i.e., dependent smoking). Less sensitive persons may acquire little or no tolerance to nicotine, remaining dependent person appears to function normally only when under the influence of nicotine. Nicotine dependent persons also report feeling “abnormal” or “not right” when deprived for more than a few hours (89,90). Although nicotine administration can cause intoxication and behavioral disruption in the nicotine naive person over time, optimal performance for most smokers on behavioral and cognitive tasks requires sustained nicotine administration, with adverse performance effects accompanying nicotine deprivation.

The nicotine withdrawal syndrome has been described in detail and includes symptoms of increased anxiety, irritability, and appetite and decreased cognitive capabilities and heart rate (72,89–95). Strong tobacco cravings are also common. Onset begins within a few hours of the last cigarette and includes an increased tendency to smoke, impaired cognitive function, and altered electrocortical function (91,92,95). Withdrawal symptoms peak within a few days and then begin to recede over the next several weeks. However, most individuals who try to quit smoking relapse before the syndrome subsides (64,95). Even the continuing smoker experiences withdrawal symptoms during each day of smoking, which presumably minimizes the duration of abstinence that can be tolerated (65).

Nicotine replacement does not appear to shorten the course of the syndrome, but it can reduce severity of the symptoms to the more tolerable levels typically observed after about 4–5 weeks of untreated abstinence. Some withdrawal symptoms, particularly cognitive impairment, cravings, and irritability, may persist for months or more in some individuals (72,95).

Smoking and Negative Mood States (96)

There is considerable evidence (97) to suggest that smoking behavior is influenced by an individual’s vulnerability to experience depressed or dysphoric mood. For example, depressive mood and a history of major depressive disorder (MDD) are more prevalent among smokers than among nonsmokers (odds ratio = 2.9; 95% CI = 1.7–4.9) (69,97–100), more tightly linked to nicotine dependent than nondependent smoking (67,99), positively related to daily cigarette consumption (100), predictive of greater withdrawal severity and withdrawal induced depressive symptoms (101,102), and associated with a decreased likelihood of quitting smoking (97,98,102,103). Moreover, most of the time (60%) this disturbance in mood precedes the development of tobacco dependence (104).

The relationship between smoking and negative affect is also similar for nonclinical disturbances of mood. For example, as shown in Fig. 3, data from the Health Promotion Disease Prevention supplement to the 1991 National Health Interview Survey (43,732 households) (105) indicate that the odds of being a smoker increase with rising levels of daily negative mood (e.g., depression, loneliness, boredom, etc.). Although the effects are significant for both sexes at the higher levels of negative mood, they are apparent sooner for women than for men. The presence of nonclinical levels of negative affect may also characterize as many as 50% of all smoking lapses (106–109). In fact, an extensive prospective study of relapse (109) showed that 19% of lapses were reported under conditions of extreme negative affect, with 62% of these episodes occurring during interpersonal conflict (arguing). Studies also show that smokers who believe that smoking is an effective affect management strategy are less likely to quit (110) and that postcessation depression and negative affect are the symptoms of withdrawal that best predict relapse (102,111–113).

Implications for Treatment

Self-Quitting in the General Population (96)

It is estimated that about 48.5% of the population of “ever” smokers (90 million people) have already stopped smoking. Unfortunately, the decline in smoking prevalence appears to have plateaued in the last 3–4 years (114). Smoking cessation continues to be a difficult proposition for most people. In the 1994 National Health Interview Supplement (NHIS-2000), it was estimated that, of the 48 million adult smokers, 69.3% want to stop smoking and Negative Mood States (96)

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![Fig. 3. Odds ratio for smoking according to negative mood score and gender.](https://academic.oup.com/jnci/article-abstract/89/24/1852/2526565)
smoking completely. Approximately 46.4% of current everyday smokers made a serious cessation attempt (stopped for at least 1 day) in the 12 months prior to the survey (11), although only 13.8% of this group, and 5.7% of all the smokers, successfully abstained from tobacco use for at least 1 month (NHIS-Health Promotion and Disease Prevention Supplement) (5). It was estimated that only 2.5% of all smokers quit smoking permanently each year (5).

It is interesting that the majority of former smokers (85%) report a preference for quitting on their own, using mostly ‘‘cold turkey’’ (85%) or gradual reduction (13%) approaches to cessation (115). Only 15% of the former smokers report using assisted or more intensive cessation treatments (e.g., physician’s advice, counseling, nicotine replacement, etc.). These findings are consistent with the suggestion that smokers are reluctant to take advantage of assisted forms of treatment when it is offered (116,117). However, the high preference of self-quitting among former smokers should not be interpreted as an endorsement for the effectiveness of a single unassisted cessation attempt. Such statistics most likely reflect the cumulative effect of multiple cessation attempts carried out over a period of several years (118), as well as the substantial economic and social barriers that reduce access to assisted forms of treatment. Indeed, in a prospective evaluation of more than 5000 would-be self-quitters, only 4.3% reported continuous abstinence 1 year after their cessation attempt (118).

Smoking Cessation Medications (119)

The understanding that tobacco addiction had a physiologic basis brought with it the implication that medications could be used to help people achieve and sustain abstinence. Two medical disorders are now widely recognized to comprise what is more generally termed tobacco addiction or dependence (89): 1) nicotine dependence and 2) nicotine withdrawal. Nicotine dependence is the disorder of maladaptive and seldom spontaneously remitting tobacco use. Diagnostic criteria for nicotine dependence include evidence of tolerance (increased use over time and absence of aversive symptoms), withdrawal (see below), and persistent desire or unsuccessful effort to reduce intake. Nicotine withdrawal is the constellation of symptoms that accompany tobacco abstinence. These symptoms can include dysphoria, insomnia, irritability, anxiety, restlessness, increased appetite, and difficulty concentrating.

Nicotine replacement. Nicotine polacrilex (‘‘gum’’) has been available as a prescription medication since 1985 in the United States and was approved for over-the-counter (OTC) marketing in early 1996. Nicotine transdermal systems (‘‘patches’’) have been available by prescription since late 1991, and two of the four systems were approved for OTC marketing in 1996. A nicotine nasal spray was approved and marketed as a prescription medication in mid-1996. In addition, in the spring of 1997, the FDA approved the nicotine vapor inhaler. All of these medications are indicated as aids to smoking cessation, and they reduce nicotine withdrawal symptoms, such as difficulty concentrating, irritability, and cravings. However, all vary somewhat in their instructions for use, side effects, dosage configuration, and the nature and extent of behavioral support programs provided by the pharmaceutical companies (65,120,121). Clinical studies in the area have concentrated almost exclusively on evaluating the long-term effectiveness of the nicotine patch and gum, and results from these studies are briefly summarized below. Further discussion is also provided in the AHCPR (i.e., Agency for Health Care Policy and Research) Clinical Practice Guideline on Smoking Cessation section (see below) and in other reviews (65,122,123).

Transdermal nicotine has been shown to be an effective form of treatment that significantly improves cessation rates across diverse settings and populations. Use of transdermal nicotine approximately doubles 6- to 12-month cessation rates in relation to the rate obtained with a comparable placebo. This result holds true, even when the patch is provided alone or paired with a low-intensity behavioral intervention. Recent meta-analyses (124) suggest that absolute cessation rates observed with the active patch may also be enhanced when it is used in conjunction with more- versus less-intense psychologic interventions, although the effect has not been uniform (125). Mean cessation rates reported in the meta-analyses for the active patch plus high-versus low-intensity psychologic interventions were 41.5% (95% CI = 37.6%–45.4%) versus 22.8% (95% CI = 21.0%–24.7%) at the end of treatment and 26.5% (95% CI = 22.6%–30.6%) versus 19.5% (95% CI = 17.2%–22.1%) at 6 months after the quit date (124).

The gum appears to improve 12-month cessation rates by 40%–60% compared with control interventions. The effect sizes for gum versus placebo or no gum conditions were higher when administered with more- versus less-intensive psychologic therapy. One analysis (126) showed no difference in 1-year abstinence rates for gum versus control conditions when each were combined with a brief behavioral intervention. Thus, unlike the patch, the gum may be less effective when only minimal forms of psychologic intervention are used; however, similar to what has been observed for the patch, cessation rates are likely to improve with increasing intensity of adjuvant therapy.

In 1994, a 4-mg dosage form of nicotine gum was approved for marketing on the basis of findings that it was effective for heavier smokers, for whom the 2-mg formulation was generally ineffective (127). Nicotine polacrilex is also the only smoking cessation medication shown to reduce reliably the weight gain associated with cessation, but the effect may not persist after polacrilex use is discontinued (65). Noncompliance with chewing frequency and use duration may reduce the gum’s effectiveness, although compliance improves with concurrent psychologic therapy (123). Moreover, the nicotine patch may be preferred to the gum, given its ease of use and constant nicotine dosing.

Negative mood, nicotine replacement, and psychotropic medication (96). As discussed above, negative mood states have a significant impact on smoking prevalence and cessation lapse. Amelioration of these conditions in the context of a smoking cessation intervention appears to be an important step in the treatment process. Some behavioral studies (128,129) indicate that smokers with high levels of precessation negative mood may benefit from cognitive-behavioral treatment that focuses directly on managing the symptoms of negative affect. For those with a history of major depression, the results of behavioral intervention alone appear less conclusive. One study (130) showed a significant benefit for a cognitive-behavioral affect
management treatment program, while another from the same laboratory (131) did not.

Studies using both the nicotine patch and the gum also show that treatment efficacy is reduced among smokers who report elevated levels of dysphoria immediately before (96,132,133) or during (111,134) the early phases of treatment. Although cessation rates can be improved to the extent that either approach offsets the increase in negative mood associated with quitting (110,133,134), the relationship may vary by level of pretreatment affect and, possibly, by sex. For example, the addition of nicotine gum to an extensive program of behavioral counseling does not appear to enhance the abstinence of smokers with a past history of MDD (131), although modest treatment gains have been reported for the combination of gum and brief counseling among those with current depressive symptoms. Combining transdermal nicotine replacement with group counseling also enhances abstinence beyond that achieved by counseling alone (96,135). Women appear to do equally well with or without the patch added to the group behavioral intervention for 2–3 months after all treatment ends. However, no effects on the basis of sex are observed at the 6-month follow-up (Cinciripini PM, Wetter DW, Cinciripini LG, Haque W, Van Unnakis H; manuscript submitted for publication). Nevertheless, this finding is interesting in view of studies that suggest that women may smoke more often than men for reasons of non-nicotine reinforcement (136) and have relapsed more in clinical trials of nicotine-replacement therapy (136) (Wetter DW, Kenford SS, Smith JJ, Fiore MC, Jorenby DE, Baker TB: manuscript in preparation).

The use of psychotropic medication as a prophylactic treatment for negative affect has also produced favorable effects on cessation rates in some studies. For example, in a preliminary report (137), abstinence was improved among smokers who reported at least one symptom of depressive mood and who took the antidepressant fluoxetine (an SSRI or selective serotonin re-uptake inhibitor). Early results with another antidepressant, nortriptyline, showed favorable effects on cessation for smokers both with and without a positive history of MDD (131). Improved levels of abstinence have also been observed among smokers with initially elevated levels of anxiety who were treated with the anxiolytic, buspirone, in conjunction with brief counseling. The drug seemed to attenuate the expected precession rise in anxiety, although the beneficial effects on abstinence lasted only for the duration of chemotherapy (138). A subsequent study (139), using considerably less provider support, found no differences with buspirone. Finally, the FDA recently approved the antidepressant, bupropion (Zyban, a dopamine reuptake inhibitor, Glaxo Wellcome), for use in smoking cessation treatment. The results of a multicenter clinical trial show that 1-year quit rates for smokers receiving 150–300 mg/day of Zyban averaged 23% versus 19% in the placebo group (140).

Experimental medications for smoking cessation (119). A variety of non-nicotine medications have also been studied and are briefly summarized below. These medications include the following: clonidine, lobeline, and mecamylamine. Clonidine, an antihypertensive, appears to be useful for some individuals, but study findings are mixed. Lobeline, which partially mimics the effects of nicotine, was used in many OTC smoking-cessation products until 1994 when the FDA removed such products from the market until they are shown to be effective. Mecamylamine, an antihypertensive that has been used in research for its nicotine blocking effects (141), enhanced cessation efforts in a preliminary study when it was co-administered with a nicotine patch (141). This drug combination will require considerable additional research to determine whether or not it is generally safe and effective, as well as to determine appropriate dosing parameters. Cotinine, a nicotine metabolite, has been evaluated in a preliminary study (143), but it is unclear whether it will prove to be efficacious for smoking cessation. More detailed reviews can be found in other sources (122,123,144).

Optimal use of approved and investigational medications would be expected to vary across patients: some may require higher doses, longer-term use, combinations of dosage forms, and possibly new dosage forms. Similarly, for people unable or unwilling to completely abstain from tobacco, experimental use of nicotine medications to treat withdrawal symptoms and to reduce their exposure to tobacco might be considered. A particularly promising application of available medications would be the combination of gum and patch, which appears to provide increased relief of withdrawal symptoms and achievement of cessation (65). Another type of combination therapy could be termed “sequential,” whereby patients use a transdermal medication to achieve abstinence and then intermittently use nicotine polacrilex as needed to sustain long-term abstinence (65).

Tobacco-derived nicotine-delivery products (119). Tobacco companies have patented a wide range of nicotine-delivering products that are most accurately considered drugs and/or drug delivery devices, regardless of how they have been or will be formally regulated (68,145). The most distinct among such tobacco company products that have actually been marketed include the Premier and the Eclipse devices of the R. J. Reynolds Tobacco Company (Winston-Salem, NC) and the Masterpiece Tobaccos chewing gum of the Pinkerton Tobacco Company (Owensboro, KY) (145,146). It is possible that some of these products would be lower in their delivery of some types of tobacco toxins. For example, Premier, and probably Eclipse, appeared lower in conventional tar but similar in nicotine and carbon monoxide delivery to a conventional cigarette and possibly higher in chemical derivatives of pyrolized glycerol. Whether or not various tobacco-caused diseases might be reduced by substitution of such products for conventional tobacco products is not known. Furthermore, the form and purpose of these products appears aimed at maintaining, if not increasing, the prevalence of nicotine dependence, whereas pharmaceutical products have been designed and marketed as means to reduce tobacco-caused disease, including nicotine dependence.

Treatment Recommendations: the AHCPR Clinical Practice Guideline on Smoking Cessation (147)

In April 1996, the AHCPR released a set of guidelines for practicing clinicians, smoking cessation specialists, and health care administrators/insurers to deliver and support effective smoking cessation interventions (123). The guideline panel evaluated more than 300 randomized controlled studies in a meta-analysis of several treatment components. The major recommendations of the panel can be summarized as follows:
1) Effective smoking cessation treatments are available, and every patient who smokes should be offered one or more of these treatments.

2) It is essential that clinicians determine and document the tobacco-use status of every patient treated in a health-care setting.

3) Brief cessation treatments are effective, and at least a minimal intervention should be provided to every patient who uses tobacco.

4) A dose–response relationship exists between the intensity and the duration of treatment and its effectiveness. In general, the more intense the intervention, the more effective it is in producing long-term abstinence from tobacco.

5) Three treatment elements, in particular, are effective, and one or more of these elements should be included in smoking-cessation treatment: (a) nicotine-replacement therapy (nicotine patches or gum); (b) social support (clinician provided encouragement and assistance); and (c) skills training/problem solving (techniques on achieving and maintaining abstinence).

6) Effective reduction of tobacco use requires that health care systems make institutional changes that result in systematic identification of, and intervention with, all tobacco users at every visit.

**Cessation screening advice and providers.** The AHCPR panel recommended that providers in primary care settings, which would include cancer screening and detection clinics, implement a systematic assessment to identify all smokers. Expanding the “vital signs” to include documentation of smoking status for every patient at every visit has been suggested for this purpose. The 4-A’s model of smoking cessation (Ask, Advise, Assist, and Arrange) was recommended as a strategy to be used by primary care clinicians (148). The model includes strong personalized messages to encourage/motivate a quit attempt and advice/information on preparing to quit and coping with withdrawal, making a commitment to abstinence, and arranging social support and follow-up. Referrals to other specialty providers are encouraged if desired by the smoker. The largest increment in success was observed after smokers were exposed to providers from multiple disciplines (e.g., medicine, psychology, and nursing).

**Intervention format: self-help or individual and group interventions.** The guideline panel noted that cessation rates attributed to different self-help modalities (e.g., books, manuals, audiotapes, community referral lists, pamphlets, etc.) did not differ appreciably from each other and that these rates were not substantially different from the rate obtained with control subjects who received no self-help material. A slight increase in cessation rates was noted in three studies that provided telephone hotline support for smoker-initiated calls (odds ratio = 1.4; 95% CI = 1.1–1.8) and in one study that combined several types of self-help materials (odds ratio = 1.9; 95% CI = 1.2–2.9). The panel recommended that telephone call-in-support be considered, if feasible, when establishing a self-help intervention program.

In contrast, interventions that offer person-to-person contact (i.e., group or individual counseling) provide a substantial treatment advantage over self-help material alone. In comparison with self-help interventions, the more time providers spend (intensity level) with smokers in a treatment session, the higher the likelihood of cessation. The highest cessation rates were observed for provider counseling sessions lasting longer than 10 minutes, but brief contact lasting 3–10 minutes, and even minimal contact lasting less than 3 minutes, progressively improved a smoker’s chance of successfully quitting over that of control subjects. In addition, both the duration of treatment and the number of treatment sessions (length of session) improved the odds of cessation, even after controlling for treatment intensity. Significant improvements in cessation were observed for interventions involving four to seven sessions carried out over an 8-week period or more.

**Treatment content.** The panel also analyzed the efficacy of several components of treatment, including aversive (rapid) smoking; setting a quit day; counseling for diet, motivation, or exercise; contingency contracting; relaxation; cigarette (brand) fading; social support; and problem solving/skills training. The results indicated that only cessation counseling, involving either general problem solving/skills training (relapse prevention, stress management, etc.) or supportive care provided by the clinician within the treatment session, significantly raised cessation rates above the rate obtained for no-contact control subjects.

The problem solving/skills approach to treatment involves such counseling elements as the recognition of high-risk situations (e.g., being around other smokers and alcohol consumption), the enhancement of coping skills designed to alter or ameliorate relapse risk (e.g., use of distraction and avoidance and planning for unanticipated events), the countering of negative mood with stress reduction and reinforcement enhancement strategies, and the provision of basic information about smoking and successful quitting (e.g., nature and course of withdrawal, the addictive aspects of smoking, etc.). The social support component refers to provider encouragement to quit (e.g., communicating confidence in the patient’s ability to quit, providing basic information about withdrawal, and providing opportunities to discuss cessation difficulties).

**Nicotine-replacement therapy.** The AHCPR panel also reviewed the results of five meta-analyses on the efficacy of the transdermal nicotine patch and three analyses focusing on nicotine gum. It was concluded that all smokers should be encouraged to use the nicotine patch or gum for smoking cessation, except in the presence of special circumstances (i.e., the need for abstinence from all sources of nicotine). Research in this area is summarized above in the “Smoking Cessation Medications” section.

In conclusion, the AHCPR guidelines provide substantial evidence that dividends in cessation success may be expected with interventions that use nicotine replacement and with interventions that last relatively longer, involve more clinical contact, and provide increasing levels of problem solving/skills training and social support. It is recommended that counseling focus on problem solving skills and social support and last as many weeks as feasible given available resources (i.e., the longer the better).
Individually Tailored Self-Help Interventions (149)

Although cessation rates associated with minimal or self-help interventions may be substantially lower than those obtained with more extensive clinical treatments, self-help programs have the potential of reaching large segments of the population at relatively low cost. It can be argued that a small treatment effect multiplied across the population can have a substantial public health impact. Moreover, recent developments in the design and implementation of new self-help materials (e.g., computer tailoring) allow more individual specificity in the treatment message than was previously possible using ubiquitous or “one size fits all” treatment materials. Personalizing or tailoring intervention materials might enhance the effectiveness of self-help approaches by focusing treatment advice on issues most relevant to the individual.

Tailored or personalized interventions incorporate information provided by the subject on certain aspects of their smoking behavior (i.e., motivation and readiness to quit, barriers to cessation, self-confidence, individual temptations, etc.) into specific written or counselor-delivered suggestions for behavior change. Early studies (150–152) in the area suggest that, when used alone or in conjunction with telephone counseling, personalized or individually tailored feedback increases cessation rates, although it may chiefly benefit smokers who are low in self-efficacy or those who are less nicotine dependent. It is important to note, however, that those who may have little intention to quit at the onset of treatment (pre-contemplators) also seem to derive an advantage from staged, matched, personalized feedback (151,153).

Tailored self-help materials have also been combined with nicotine-replacement therapy, using nicotine polacrilex gum and the transdermal nicotine medications. The combination of these two approaches presents a substantial research and public health opportunity given the preference of many smokers for minimal intervention and the documented effectiveness of nicotine replacement (see section on AHCPR recommendations). Both the patch and nicotine gum are now available as OTC medications, and some pharmaceutical companies (e.g., SmithKline Beecham and McNeil Pharmaceuticals, Philadelphia, PA) provide self-help materials to product consumers. Given the widespread distribution of OTC medications, plus consumer advertising to spur interest in use of the product, the combination of nicotine-replacement therapy and tailored self-help materials provided by the manufacturers could become part of the routine care provided for smoking cessation. Outcome research using such approaches is just beginning. For example, a study by Orleans et al. (154) used a series of tailored letters to supplement the use of transdermal nicotine replacement in a population of elderly smokers. Preliminary results from this randomized trial suggest that the 3-month point prevalence abstinence rate among patch users receiving the tailored program was 67% in comparison with an abstinence rate of 32% among patch users receiving nontailored support. High levels of initial abstinence (44%) have also been reported (149) among users of the nicotine patch and the Committed Quitters Personal Support Program (CQ), the self-help program provided with the Nicoderm prescription patch (SmithKline Beecham Consumer Healthcare). Participants in the CQ program were mailed sequential letters, calendars, and postcard reminders tailored to selected cessation benefits and barriers that were identified in a baseline interview. They also received a follow-up telephone call within a day or two of their quit date and again 5 weeks later. While promising, the results of this program, as well as of others associated with OTC nicotine-replacement products, require further evaluation in randomized clinical trials.

Community Intervention (COMMIT) (155)

The treatment approaches discussed thus far target the behavior of individual smokers and measure the success of the intervention in terms of the abstinence achieved by these smokers at specific points in time. Community interventions, on the other hand, expose entire communities to a cessation or prevention treatment and measure treatment outcome in terms of differences in smoking prevalence between exposed and unexposed communities. Recently, a combination of community-based interventions to help smokers quit was evaluated in COMMIT, which was funded by the NCI. COMMIT was a large-scale trial involving 11 matched pairs of communities in North America (156) randomly assigned to receive either an active community intervention or no active intervention (control).

A baseline survey, using random-digit-dialing methods, was used to estimate the smoking prevalence in each community and to identify cohorts of heavy (≥25 cigarettes/day) and light-to-moderate smokers (<25 cigarettes/day) to be followed. After the randomization, the COMMIT intervention was implemented in the intervention communities by use of several existing community channels: media and public education, health care providers, worksights (and community organizations), and cessation resources (156,157). The assumption was that the combination of approaches would be more effective than the sum of its individual component effects. COMMIT would act as a “catalyst” for smoking cessation activities in the community.

The primary hypothesis of COMMIT was that the community-level, multi-channel, 4-year intervention would increase quit rates among cigarette smokers (with particular interest in heavy smokers). “Quit rate” was defined as the fraction of cohort members who had achieved and maintained cessation for at least 6 months at the end of the trial. End point cohorts totaling 10,019 heavy smokers and 10,328 light-to-moderate smokers, 25–64 years of age, were followed by telephone contact (157). The cohort analysis showed that the mean heavy smoker quit rate was 18% for the intervention communities versus 18.7% for the comparison communities, a nonsignificant difference (P = .68). Significant group differences (P = .004) were observed for corresponding light-to-moderate smoker quit rates, averaging 30.6% and 27.5% for the intervention and control communities, respectively. No significant sex differences in the effect of the intervention were noted. However, among light-to-moderate smokers, the less-educated subgroup appeared to be more responsive to the intervention than college-educated smokers. Analysis of the cross-sectional survey data also showed a nonsignificant difference in the decline in smoking prevalence between the intervention and the comparison communities, with declines of 3.5% and 3.2% observed, respectively. There was an encouraging decrease in smoking prevalence for middle-aged and older adults, but the youngest group, ages 18–24 years, unfortunately showed a much smaller change (157,158).
The impact of this community-based intervention on light-to-moderate smokers, although modest, has public health importance. That this community-based intervention did not affect heavy smokers or have a substantial impact on smoking prevalence beyond favorable secular trends, while disappointing, points to the need for the prevention of nicotine dependence and for more extensive treatment of highly nicotine-dependent smokers. Such treatment approaches may go beyond traditional educational and minimal levels of intervention and incorporate the type of provider support, skills-training techniques, and nicotine-replacement therapies recommended in the AHCCPR guideline (123) and may include alternative pharmacologic intervention as well.

Implications for Public Policy

Regulatory Aspects of Prevention: Role of the FDA
(Remarks from former FDA Commissioner David Kessler) (159)

To reduce the initiation and use of tobacco by young people, the Food and Drug Administration (FDA) launched an investigation to answer two questions: Can nicotine be considered a drug under the Federal Government’s Food, Drug and Cosmetics Act? If so, what is the appropriate strategy to regulate this drug?

Evidence that nicotine can be considered a drug. The Federal Government’s Food, Drug and Cosmetics Act defines a drug as “an article (except for food) intended to affect the structure and function of the body.” The scientific literature demonstrates that nicotine in cigarettes and smokeless tobacco has such an effect on the body. Since the early 1990s, there has been almost universal agreement within the scientific and medical communities that nicotine is an addictive drug.

During its investigation, the FDA discovered that the tobacco industry also knew about nicotine’s addictive properties. In the early 1980s, Phillip Morris (New York, NY) forced one of its scientists, Dr. Victor DeNoble, to withdraw a manuscript he had submitted to the Journal of Psychopharmacology. Dr. DeNoble had found that rats will self-administer nicotine, one of the hallmark properties of an addictive substance, and conducted tests on nicotine analogues to find a substitute that could duplicate nicotine’s psychoactive and reinforcing effects.

However, to consider nicotine a drug, the FDA also had to have evidence of intention to produce nicotine’s pharmacologic effects. The FDA uncovered 30 years of industry documents that describe research by the tobacco industry to understand the pharmacology of nicotine, including the minimum dose needed to satisfy smokers. Specifically, the internal documents from Phillip Morris and Brown & Williamson (Louisville, KY) revealed that both companies conducted research on nicotine pharmacology and manipulation and acknowledged nicotine’s central role in sustaining tobacco use. For example, the industry found it could increase the amount of nicotine in a cigarette by using high-nicotine tobacco and adding lentic acid to mask the harsh flavor of high-nicotine tobacco. One company’s handbook on leaf blending and product development also describes how the industry uses ammonia to “liberate free nicotine from the blend, which is associated with increases in impact and satisfaction reported by smokers.”

Evidence that tobacco is marketed to youth. The second phase of the FDA investigation examined the way the tobacco industry markets its products to young people. An internal R. J. Reynolds (RJR) document reported that “evidence is now available to indicate that the 14–18 year old group is an increasing segment of the smoking population. RJR [team] must soon establish a successful new brand in this market if our position in the industry is to be maintained over the long term.” RJR later introduced the Joe Camel character. The FDA found that Joe Camel promotional items played a central role in RJR’s YAS (Young Adult Smokers) program.

Strategy to reduce tobacco use by youth. On the basis of this evidence, the FDA developed the following two-pronged strategy to regulate the sale and marketing of tobacco products to youth:

1) Minimize access by restricting the sale of cigarettes and tobacco to face-to-face transactions and by banning the distribution of tobacco in vending machines, mail-order sales, self-service displays, and free samples.
2) Minimize the impact of tobacco advertisements that play on the themes of fun, rebellion, glamour, freedom, and independence—themes with particular appeal to adolescents.
3) Ban outdoor advertising within 1000 feet of playgrounds and schools and restrict all other advertising to black and white, text-only format to reduce imagery that appeals to youth.
4) Eliminate brand name promotions on nontobacco items (e.g., hats and t-shirts).
5) Limit the sponsorship of sporting and cultural events by tobacco companies to the use of the corporate name, not the brand name.

National Strategies to Combat Tobacco Use and Addiction
(Remarks from former Surgeon General C. Everett Koop) (160)

Nicotine regulation will play a major role on the part of government, the health care community, and society at large in the near future. As described above, the demand that the Food and Drug Administration be involved in regulating nicotine has been intensified because of the recently publicized reports that cigarette companies manipulate nicotine levels to ensure a nicotine level sufficient to create and sustain addiction. But, winning the war against the tobacco industry and against nicotine addiction will require more than a regulation of nicotine. It will require a variety of strategies aimed at reducing the demand for smoking by:

- Changing public attitudes about tobacco, the tobacco industry, and tobacco addiction.
- Despoiling the myth of the economic necessity of tobacco and impressing on the public the hypocrisy of allowing tobacco companies to export tobacco while the U.S. takes actions against other countries that import cocaine to our country;
- Broadening the legal attack on the tobacco industries and their advertising practices, especially those directed to youth; and
Taking a more active role in prevention in the healthcare arena.

**Changing public attitudes.** More action can be taken in this regard to improve the dialog between smokers and nonsmokers and encourage third-party payers to support smoking-cessation programs. Many insurance companies still will not pay a mere $50 to help a patient participate in a smoking-cessation program, although they willingly pay huge sums for medical care related to smoking-induced illness. Thoughtful and effective ways to deal with the issue of nicotine addiction are needed.

**Despoiling the myth of tobacco economics.** Clear, long-range strategies to deal with the economic myths and realities of tobacco are also needed. Despite the argument that tobacco restrictions would have a negative effect on the American economy, a number of studies have shown that this is not the case. Moreover, the right of a few individuals to profit from a product that kills many of their fellow citizens every year is questionable. Clearly, tobacco is costing the individual tobacco producing states and country more than it profits either one.

**Broadening the legal attack on the tobacco industry and tobacco advertising.** Although the recent, large, class-action suit (Costanzo) met a discouraging setback, State suits aimed at recovering Medicaid expenditures on smoking-related disease may eventually prevail (see Authors’ note below). It may yet be possible to win a successful liability lawsuit against a tobacco company.

**Focusing physicians on tobacco-addiction prevention.** Finally, American physicians need to be encouraged to be more effective in their intervention with both their nonsmoking and their smoking patients. Doctors need to take advantage of every professional encounter with a patient to intervene against smoking in that patient’s life or in the life of a family member.

**Author's Note**

Before publication of this article, negotiations between State Attorneys General and tobacco companies resulted in a pending legislative proposal for Congressional consideration. Included in this complex settlement are provisions to restrict the advertising and sales of tobacco, to restrict smoking in public places, to penalize tobacco companies if youth smoking rates are not reduced, and to require stronger warning labels on tobacco products. Tobacco companies have also agreed to provide funds for medical research, smoking-cessation programs, public education about tobacco, and enforcement of the settlement provisions. The medical research funds alone would total $25 billion over 8 years.

Drs. C. Everett Koop and David Kessler chaired a committee of public health experts convened to advise the Congress about the settlement. Their committee recommended many modifications and additions to the settlement. In particular, they recommended that the FDA retain the ability to regulate the nicotine content of cigarettes and that the penalties be increased for tobacco companies if youth smoking rates do not fall. The committee proposed even larger budgets for the public health and research programs in the settlement. They also suggested provisions to help tobacco farmers convert to other crops and to reduce tobacco use in other nations. Currently, the U.S. Department of Health and Human Services is conducting a complete review of the settlement to make recommendations to the President.

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**Appendix Table 1. Conference participants**

<table>
<thead>
<tr>
<th>Participant</th>
<th>Institution</th>
</tr>
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<tbody>
<tr>
<td>Neal Benowitz</td>
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<td>Stephen Hecht</td>
<td>University of Minnesota Cancer Center, Minneapolis, MN</td>
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<tr>
<td>Jack Henningfield</td>
<td>The Johns Hopkins University, and Pinney Associates, Baltimore, MD</td>
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<tr>
<td>Dietrich Hoffmann</td>
<td>American Health Foundation, Valhalla, NY</td>
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<tr>
<td>David Kessler</td>
<td>Food and Drug Administration, Washington, DC</td>
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<td>C. Everett Koop</td>
<td>National Cancer Institute, Bethesda, MD</td>
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<td>Barnett Kramer</td>
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<td>Marc Manley</td>
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<td>Margaret Spitz</td>
<td>The University of Texas, M. D. Anderson Cancer Center, Houston, TX</td>
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<td>Victor Strecher</td>
<td>University of Michigan Cancer Center, Ann Arbor, MI</td>
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<tr>
<td>Ernst Wynder</td>
<td>American Health Foundation, Valhalla, NY</td>
</tr>
</tbody>
</table>

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Notes

1Cigarette pack-years = the number of packs of cigarettes smoked per day multiplied by the number of years of smoking.

Editor’s Note: Because B. S. Kramer, Editor-in-Chief of the Journal, is one of the authors of this article, a member of the Editorial Board who is not directly affiliated with the National Cancer Institute or with the American Society of Clinical Oncology served as acting Editor-in-Chief.

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