Developing Consensus on Tobacco Control and Research

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In June 2006, the National Institutes of Health (NIH) held its first State-of-the-Science Conference on tobacco control and prevention titled, Tobacco Use: Prevention, Cessation, and Control. State-of-the-Science Conferences are convened as part of the NIH Consensus Development Program, to form "unbiased, independent, evidence-based assessments of complex medical issues."[1] The NIH Consensus Statements and State-of-the Science Statements produced by these Conferences are disseminated widely to healthcare practitioners, policymakers, patients, the media, and the general public. Since the program's inception in 1977, NIH has held more than 130 such Conferences.

The State-of-the-Science Conference on the prevention, cessation, and control of tobacco was sponsored by the NIH Office of Medical Applications of Research, the National Cancer Institute (NCI), and twelve other NIH Institutes and Centers (ICs) along with six other federal agencies that served as conference partners.[2] Together, the co-sponsoring and partner agencies formed a planning group that determined the six questions to be answered by the Conference:

1. What are the effective population- and community-based interventions to prevent tobacco use in adolescents and young adults, including among diverse populations?
2. What are the effective strategies for increasing consumer demand for and use of proven, individually-oriented cessation treatments, including among diverse populations?
3. What are the effective strategies for increasing the implementation of proven, population-level, tobacco-use cessation strategies, particularly by healthcare systems and communities?
4. What is the effect of smokeless tobacco product marketing and use on population harm from tobacco use?
5. What is the effectiveness of prevention and of cessation interventions in populations with co-occurring morbidities and risk behaviors?

6. What research is needed to make the most progress and greatest public health gains nationally and internationally?

Given the focused nature of the process, the Conference questions were not designed as a comprehensive assessment of tobacco control and prevention; rather they were intended to address a small number of priority issues.

The strength of the Consensus Development Program lies in its objectivity, independence, and its focus on specific, predetermined questions. State-of-the-Science panel members are drawn from physicians, scientists, and representatives of the public, **from outside the field to be evaluated**; they may not have scientific or financial conflicts of interest, hold advocacy opinions relevant to the Conference, or be employed by the U.S. Department of Health and Human Services (USDHHS). Panel members are not known to the co-sponsoring ICs and partners prior to the Conference, and interaction between panel members and co-sponsors or partners before or during the Conference is prohibited. A range of expertise on the panel contributes to its ability to deliberate thoughtfully on the scientific material presented; panel members are reimbursed for their travel expenses, but otherwise receive no payment for their work. Conference statements represent an independent report of the Conference panel and are not policy statements of the NIH or the U.S. Federal Government.

Being a member of a Consensus Development Panel is a very large responsibility. Panel members prepare for the Conference by studying a systematic literature review, prepared under contract to Agency for Healthcare Research and Quality (AHRQ) by RTI International–University of North Carolina Evidence-Based Practice Center, on the questions they will be asked to address.[3] This literature review is made available to the public at the end of the Conference. Over the course of the public portion of the Conference, the panel hears presentations from invited experts as well as questions, comments, and statements from members of the public. Additionally, the panel receives and reviews comments sent by e-mail, for those attending the conference via the Internet. Following the conclusion of the public session, panel members begin their closed deliberations, to together develop their Conference State-

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ment. It is not uncommon for a panel to work through the night to reach consensus and finalize their statement, which is released to the conference attendees, the media and the general public on the morning of the next day.

The NIH State-of-the Science Conference on Tobacco Use was attended by more than 400 people from 21 countries, either in person or via the live webcast. The Conference Panel was chaired by David Ransohoff, MD, Professor of Medicine at the University of North Carolina at Chapel Hill School of Medicine. Other members of the panel included experts in the fields of medicine, general and pediatric psychiatry, addiction medicine, nursing, social work, population science, cancer prevention, minority health and health disparities, clinical study methodology, and clinical epidemiology, as well as a representative of the public. Invited experts from pertinent fields made presentations at the Conference, focusing their remarks on information the Conference Panel needed to answer their assigned questions. Additionally, more than 130 written comments and statements were received and reviewed by the Conference Panel.

Following an intense night of deliberation, the panel's Conference Statement was presented to the public on June 14, 2006. The Statement outlined what, in the view of the panel, we know and what we need to learn for each of the questions the panel was asked to address. The overall conclusion as published on the *Annals of Internal Medicine* website is below[4]:

"Tobacco use remains a very serious public health problem. Coordinated national strategies for tobacco prevention, cessation, and control are essential if the United States is to achieve the *Healthy People 2010* goals.[5] Most adult smokers want to quit, and effective interventions exist. However, only a small proportion of tobacco users try treatment. This gap represents a major national quality-of-care problem. Many cities and states have implemented effective policies to reduce tobacco use; public health and government leaders should learn from these experiences.

Because smokeless tobacco use may increase in the United States, it will be increasingly important to understand net population harms related to use of smokeless tobacco. Prevention, especially among youth, and cessation are the cornerstones of strategies to reduce tobacco use. Tobacco use is a critical and chronic problem that requires close attention from healthcare providers, healthcare organizations, and research support organizations."

Our nation has made enormous progress in reducing tobacco use, preventing the premature deaths of literally millions of Americans. Since the release of the first Surgeon's General report on smoking in 1964,[6] adult smoking prevalence has been cut in half, from about 42% in 1965 to 21% in 2005.[7,8] Nonetheless, as the Conference Statement noted, "tobacco use **remains** a

very serious public health problem" (emphasis added). The panel identified numerous areas for future research including:

Improving and implementing effective interventions such as increasing and sustaining demand for smoking-cessation treatment, examining components of telephone-based counseling programs, and developing and enhancing both pharmacologic and non-pharmacologic treatments.

Improving and implementing effective policies such as identifying barriers to implementing successful comprehensive tobacco-control programs, developing effective policies for reimbursing healthcare providers, and conducting economic studies to tobacco prevention, cessation, and control.

Developing new population- and community-based interventions such as evaluating social marketing strategies, learning from natural experiments, determining the effectiveness of interventions in various settings, and evaluating approaches to reduce tobacco use in vulnerable populations.

Conducting research on smokeless tobacco including impact of marketing, measuring nicotine and toxins, evaluating advantages and disadvantages of regulation, and assessing cancer and other disease risks.

The Conference Statement on Tobacco Use represents the culmination of a lengthy effort by an independent, unbiased panel of scholars who have not previously considered the issue of tobacco use. It is hoped that their diligent efforts, as well as this supplement to the *American Journal of Preventive Medicine*[9–20] containing articles from many of the Conference's invited experts, will bring new energy, ideas and enthusiasm to reducing our nation's burden of tobacco use.

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Charting the Science of the Future
Where Tobacco-Control Research Must Go

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The state of the science of tobacco control is, in a word, impressive. In fields ranging from epidemiology to biology, from psychology to operations research, from brain chemistry to economics, research on tobacco use, prevention, cessation, and control has had a profound impact on the public's knowledge and practices regarding the single greatest behavior-related cause of illness and death. The behavioral response, in turn, has generated an enormous public health benefit in the form of large reductions in avoidable illness, disability, and premature mortality.

The heart of the science lies in the original epidemiology in the 1950s that established cigarette smoking as the principal cause of lung cancer.[1–5] That work forever altered the world's perception of smoking. Even though it was applied research, it helped to define the very field of epidemiology and elevated its stature in a world of medical science previously slavishly devoted to germ theory, laboratory analysis, and pure clinical observation.[6]

More recently, epidemiologic science has fed the increasing demand for smoke-free environments. Beginning with Hirayama's ground-breaking study of lung cancer in the nonsmoking wives of smoking husbands,[7] this body of work[8] has established the scientific basis for what is now a profusion of smoke-free laws throughout the United States (more than half of the states now ban smoking in all workplaces, including all restaurants and bars) and countries of the world (more than a dozen at this count). The other crucial line of research with regard to secondhand-smoke exposure—work demonstrating that restaurants and bars that go smoke-free do not suffer financial losses as a result[9]—is itself a form of epidemiology typically utilizing a case–control method (i.e., comparing sales in establishments in newly smoke-free jurisdictions with sales in establishments in jurisdictions lacking smoke-free policies).

Biological, behavioral, and social sciences have contributed mightily as well, ranging from the development of novel smoking-cessation treatments and trials demonstrating their efficacy[10] to economic analysis that has made taxation a cornerstone of sound tobacco-control policy worldwide.[11] Indeed, most of what we know about tobacco and health and effective tobacco control derives from research pursued for more than a half century now. This is without doubt one of history's greatest public health research success stories.[12,13] The articles in this supplement to the *American Journal of Preventive Medicine*[14–25] vividly illustrate the wealth of research-based knowledge on multiple important subjects related to tobacco use, prevention, cessation, and control. The tremendous public health impact to which that explosion of knowledge has contributed is reflected in data on smoking prevalence and outcome: the former has declined in the U.S. by more than half since its peak in the early 1960s, with the consequence that perhaps 3 million Americans have avoided premature smoking-related deaths.[12]

And yet, the glass remains half empty.[13] If progress against smoking ranks as the developed world's greatest public health achievement in the past half-century, as I would contend, smoking also remains unarguably the greatest cause of premature death. That the rate of decline in smoking has slowed substantially in affluent countries, and has actually risen slightly in a few, is a source of great concern. That the "brown plague" is metastasizing throughout the developing world is frightening and, given the role of the multinational tobacco companies, unconscionable.

The future of tobacco control will never rest solely on the development of new research-based knowledge; it never has. Almost certainly the future will depend far more on effective politics and activism. Still, science can and must continue to contribute. In developing countries, reproduction of basic epidemiology and social science research will be essential to contextualize the problem and make it relevant to policymakers. In the developed world, the issues demanding attention are, in many ways, far more complicated than those that confronted earlier generations of tobacco-control researchers. So too will be the science needed to resolve them.

I leave the hard task of formulating that science to others. Here I will simply identify some of the challenging issues with which, collectively, we will have to grapple.

First and foremost is the question of "what's next" in tobacco control in affluent countries. Scores of studies

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have documented the reduction in smoking produced by taxation; smoke-free indoor-air policies; sizable, sustained, professionally-developed countermarketing campaigns; and bans on tobacco advertising and promotion.[12] But what do you do after you have implemented all of these policies? Consider the case of Ireland, the first country to adopt a comprehensive smoke-free workplace policy. Today the price of cigarettes in Ireland exceeds $9 a pack. With the exception of point-of-sale, virtually all forms of tobacco advertising and promotion are banned. (The Irish authorities are targeting point-of-sale advertising now.) Before implementation of the smoke-free workplace law, smoking prevalence exceeded 25%. A year later it had dropped to 23%. One year thereafter it was back up to 25%.[26] The Irish could benefit from a large and sustained norm-changing media campaign. But short of banning smoking anywhere in public, what are public health officials to do to combat the ongoing scourge of tobacco in Ireland?

Similar problems are seen emerging in many countries, including the U.S., in which the decline in smoking has slowed and threatens to level off. To be sure, pockets of success give reason for hope—California recently reported a decline in adult daily smoking to below 10%[27]—but one senses considerable pessimism about the potential to sustain substantial progress against smoking.

In part, this reflects diminished resources and diminished expectations about resources. The entire field of public health was deeply disappointed by the failure of the states to use Master Settlement Agreement allotments to fund comprehensive tobacco-control programs. Long-time champions of tobacco control research, most notably the Robert Wood Johnson Foundation, have moved on to other issues. The challenge of making tobacco-control research, a now "aging" field, fresh, relevant, and compelling to the new generation of funders must be confronted.

More fundamentally, however, the slowing of progress against smoking reflects a fact that is frequently acknowledged but then seemingly forgotten when policies and interventions are designed and when the future of tobacco control is contemplated: today's smokers differ from the smokers of "yesteryear," many of whom have quit. Some in the remaining smoking population—possibly a sizable proportion—may be true "hardcore smokers," those who are unable or unwilling to quit and likely to remain so.[28] But in my judgment, the most important fact about today's smokers is that many of them—perhaps as many as half—are suffering from some form of mental illness or (other) substance abuse.[29] As a group, they find quitting more difficult, and perhaps of less interest. For many, the behavior of smoking is not simply a matter of addiction, nor one of self-image; rather, many of today's smokers are self-administering nicotine, and perhaps other chemicals in smoke, to treat symptoms of their comorbidities. We ignore this at our peril, and theirs. Increasingly, tobacco-control policies and smoking-cessation treatments must focus on addressing the needs of this growing population who smoke to deal with a variety of problems that may have had little relevance to previous generations of smokers who quit relatively easily.

Speaking of smoking-cessation treatments, new ones must be found that are more effective. That could mean simply more effective medications. But it also likely means two other things. First, it means developing products that are effective in everyday practice. There is a small but thought-provoking literature that questions whether over-the-counter (OTC) nicotine replacement therapy (NRT) products actually work in everyday settings, as opposed to the carefully controlled and monitored clinical trial research that has found them efficacious.[30] Given increasing attention devoted to finding ways to get more NRT products in the hands (and in the mouths and on the arms) of smokers, it is crucial to understand whether OTC products do work, and if so, how well.

The second implication, closely related to the first, is that cessation products that are far more attractive to smokers than today's offerings need to be designed. To get over the hurdle of U.S. Food and Drug Administration (FDA) regulation, many NRT products have been intentionally designed to be consumer-unattractive. To win FDA approval, the original nicotine "gum" was designed to taste bad and, of course, not to be addictive. Yet cessation products have to compete with smoking, an obviously attractive, even seductive, product.

So how does one create a treatment product that can compete with cigarettes? That question raises others: how can a timid FDA be brought to recognize that, if we are to get serious about fighting smoking, the agency may need to authorize new products that pose risks currently deemed unacceptable? Would a true pulmonary nicotine inhaler, certain to sustain addiction, be a bad thing when dealing with the most hardcore of nicotine addicts?

Questions such as this one inevitably lead to the issue that, in my 30 years in tobacco control, I have found the single most perplexing: "tobacco harm reduction."[31] The debate on harm reduction generates its own set of challenging questions: Should products less hazardous than cigarettes, including tobacco products, be promoted as alternatives to smoking for smokers who are unable, or unwilling, to quit? If so, is it possible to target promotion so finely, thereby avoiding encouraging others to use a product, still risky, when otherwise they would have abstained entirely? What kinds of products should be considered as acceptable members of the tobacco harm reduction arsenal? For example, is it advisable to promote low-nitrosamine smokeless tobacco products as much less hazardous than cigarettes (which they certainly are[32])? How can the population

impact that would follow from the introduction and promotion of ostensibly less hazardous products be assessed? What surveillance system could evaluate use patterns, and ultimately health consequences, when confronted with possibly a dozen or more qualitatively different types of products and the hundreds of mixed use patterns that would emerge? Indeed, short of waiting 30 years for the (possibly inadequate) epidemiologic evidence, how can risk reduction potential be evaluated scientifically? The questions are endless, with none of them lending themselves to easy resolution. Yet "harm reduction" may be an important wave of the future. Will it join prevention, cessation, and protection of others as the fourth pillar of comprehensive tobacco control?

The most important questions about the future of tobacco control include some that have challenged us for decades. How can we prevent children from experimenting with cigarettes, and, for many, going on to become addicted smokers? Sadly, knowledge in this all-important domain is sorely lacking. Clearly we need far better understanding of what motivates youthful experimentation with tobacco, and—more importantly, I believe—what converts experimentation into long-term smoking. And then we need to understand how to intervene to prevent the latter, if not the former. While probing the depths of behavioral research, we should also urge basic science and laboratory colleagues to seek the Holy Grail of smoking prevention: a vaccine that would prevent the onset of addiction.[33]

And perhaps most importantly, as we look to the future, how can we, as a global tobacco-control community, reduce the toll that the World Health Organization foresees for tobacco in the present century? During the course of this century, WHO predicts that, without changes in currently anticipated trends, tobacco will kill one billion citizens of the globe.[34] That is an unimaginable disaster. The Framework Convention on Tobacco Control,[35] a global treaty based on tobacco-control science, now ratified by 148 countries, provides a vehicle to avoid much of that disaster. But how, and how well, will we implement its important life-sparing provisions?

The state of the science of tobacco control is indeed impressive. So too are the challenges confronting it for the future.

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The Tobacco Epidemic in the United States

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Abstract: Tobacco use, primarily in the form of cigarettes and exposure to tobacco smoke pollution, has caused the premature deaths of more than 14 million Americans since 1964. The major diseases caused by tobacco and tobacco smoke include lung cancer, other cancers, coronary heart disease, other cardiovascular diseases, chronic respiratory diseases, pregnancy complications, and respiratory diseases in children. Per capita consumption of various tobacco products has declined substantially since 1950, with current consumption at approximately 3.7 pounds per capita. Whereas approximately two in five adults smoked cigarettes in 1965, approximately one in five did so in 2005.

Several factors can influence initiation and cessation, including product factors (e.g., ventilation holes, additives, and flavorings); host factors (intention to use, level of dependence); tobacco company activities (e.g., marketing strategies, efforts to undermine public health activities); and environmental factors (e.g., peer and parental smoking, smoke-free air laws and policies). Efforts to prevent initiation, promote quitting, and protect nonsmokers should reduce exposure to pro-tobacco marketing and increase (1) the price of tobacco products, (2) protection from tobacco smoke pollution, (3) effective mass media strategies, (4) provision of effective cessation support, (5) effective regulation, and (6) litigation that holds the industry responsible for its misdeeds. Adequate implementation of effective tobacco-control strategies and useful scientific advances will help to ensure that per capita consumption decreases to the lowest level possible. The economic benefits of tobacco in our society are replaceable and they pale in comparison to the extent of human life lost.
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Introduction

Tobacco use, primarily in the form of cigarettes, has caused more than 14 million premature deaths in the United States since 1964.[1,2] It remains the single leading preventable cause of death in this country, with 400,000 current and former smokers dying annually from smoking-attributable diseases, and 38,000 nonsmokers dying annually because of exposure to tobacco smoke pollution.[2,3] Approximately 8.6 million Americans live with serious disease(s) caused by their smoking.[4] Peto and his colleagues[5] estimate that one half of all smokers, especially those who began as teens, can expect to die of tobacco use. Of these, approximately one half will die in middle age, losing an average of 20–25 years of life expectancy.

This article provides an overview of the consequences and patterns of tobacco use, factors that can influence use, and efforts to control use. It documents the tremendous progress that has been made in reducing use and discusses factors that either can promote or reduce use. A final section will describe possible future scenarios of tobacco consumption and discuss some economic considerations that would arise if U.S. consumption is reduced substantially.

Consequences of Tobacco Use and Exposure to Secondhand Smoke
Active Cigarette Smoking

Using criteria that were described in the initial report of the Advisory Committee to the U.S. Surgeon General and later elaborated upon by A.B. Hill, scientists have documented a list of diseases for which sufficient evidence exists to conclude that they are caused by cigarette smoking (Table 1).[1,6–8] Tobacco use remains the single leading preventable cause of death in the U.S.[3] Nearly one of every five deaths in the U.S. is caused by cigarette smoking.[2]

Cigarette smoke contains 4800 identified chemicals, at least 250 of which cause cancer or are toxic in other ways.[9,10] Hecht[11] estimates that 61 chemicals in tobacco smoke cause cancer, with polycyclic aromatic hydrocarbons, nitrosamines, and aromatic amines being major contributors. Carbon monoxide and other chemicals in tobacco smoke contribute to processes leading to car-

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Table 1. Diseases/conditions caused by active cigarette smoking[1]

Disease	Effects
Malignant neoplasms	Cancers of the lung, larynx, mouth, esophagus, urinary bladder, pancreas, kidney, cervix uteri, stomach, and acute myeloid leukemia
Cardiovascular diseases	Coronary heart disease, cerebrovascular disease, atherosclerosis, and aortic aneurysm
Respiratory diseases in adults	Chronic obstructive pulmonary disease (bronchitis, emphysema, chronic airway obstruction), pneumonia, premature onset of and an accelerated age-related decline in lung function, all major respiratory symptoms (e.g., coughing, phlegm, wheezing, dyspnea), poor asthma control
Respiratory diseases in young people	Impaired lung growth, respiratory symptoms, and asthma-related symptoms (e.g., wheezing) in childhood and adolescence; early onset of lung function decline during late adolescence and early adulthood
Reproductive and perinatal conditions	Sudden infant death syndrome, reduced fertility in women, fetal growth restriction, low birth weight, premature rupture of the membranes, placenta previa, placental abruption, preterm delivery and shortened gestation, respiratory distress syndrome
Miscellaneous	Cataracts, hip fractures, low bone density, peptic ulcer disease in persons who are Helicobacter pylori positive, diminished health status (i.e., increased absenteeism from work, increased use of medical care services); adverse surgical outcomes related to wound healing and respiratory complications

diovascular disease, such as endothelial injury and dysfunction, atherosclerosis, platelet aggregation, thrombosis, low-grade inflammation, and increased levels of carboxyhemoglobin.[1] Active smoking induces processes such as oxidative stress, inflammation, and protease–antiprotease imbalances that injure airways and alveoli and if sustained contribute to chronic obstructive pulmonary disease.[1] Smokers of light and ultralight cigarettes are at the same risk for diseases as smokers of full-flavor cigarettes.[1,12] This is true despite the published tar yields for light and ultralight cigarettes that inaccurately suggest that smokers are exposed to lower concentrations of toxic chemicals. The published tar yields are based on the Federal Trade Commission (FTC)'s testing method, which does not reflect actual human smoking patterns.[13] Hecht and his colleagues[14] have demonstrated similar uptakes of lung carcinogens

and nicotine among smokers of ultralight, light, and full-flavor cigarettes.

Use of Other Tobacco Products

Cigar smoke is composed of the same carcinogenic and toxic constituents as in cigarette smoke.[15] Regular cigar smoking causes cancers of the oral cavity, larynx, esophagus, and lung. Heavy cigar smokers and those who inhale deeply are at increased risk of coronary heart disease and chronic obstructive pulmonary disease. Pipe smoking increases the risk of cancers of the oral cavity, larynx, esophagus, and lung, as well as of chronic obstructive pulmonary disease.[16] Use of smokeless tobacco (such as snuff and chewing tobacco) causes cancer of the oral cavity and increases the risk of oral leukoplakia and gingival recession.[10,17,18] As Hatsukami and her colleagues[19] discuss in this issue, many different forms of smokeless tobacco exist, with variability in the levels of toxins. The available scientific literature suggests that disease risk may also vary by product type.[19,20]

Bidis are small, thin, hand-rolled cigarettes consisting of tobacco wrapped in a tendu or temburni leaf and wrapped in a string.[21,22] In studies from India, bidi smoking has been associated with increased risk of cancers of the oral cavity, esophagus, stomach, and lung, as well as of coronary heart disease and chronic bronchitis.[23–26] Also known as clove cigarettes, kreteks contain tobacco, clove, and other additives.[27] Eugenol, a product of the clove buds, is a mild anesthetic that permits deeper inhalation.[28] Kretek use increases the risk of acute lung injury, especially among individuals with asthma or respiratory infections; it also increases risk of abnormal lung function.[27,29]

Addiction

Because they contain nicotine, all tobacco products produce addiction.[30] The pharmacologic and behavioral processes that determine addiction to tobacco products are similar to those that determine addiction to illicit drugs such as heroin or cocaine.[30] The tobacco industry is capable of manipulating the bioavailability and reinforcing properties of nicotine,[31–33] even modest exposure of which can initiate the dependence process.[34–37]

Involuntary Exposure to Tobacco Smoke Pollution

The smoke emanating from the tip of a burning tobacco product is called sidestream smoke; the smoke that the smoker inhales is called mainstream smoke.[38] Sidestream smoke and exhaled mainstream smoke are the main contributors to the tobacco smoke pollution that is often inhaled involuntarily by nonsmokers and is also known as secondhand smoke and environmental
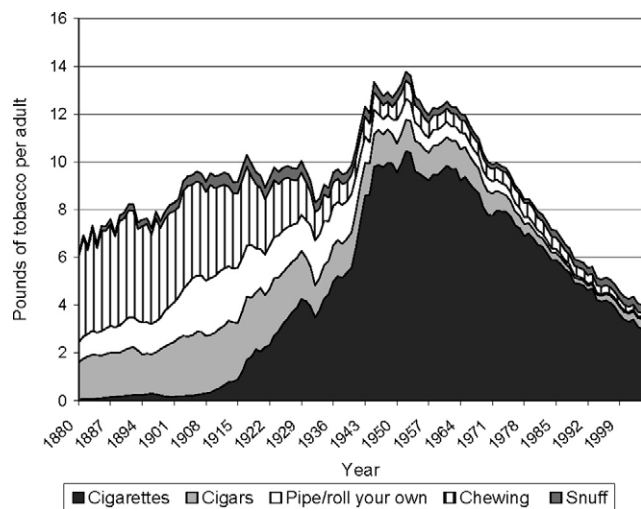
Figure 1. Trends in per capita consumption of various tobacco products—United States, 1880–2004.[39,40,45,46] Source: United States Department of Agriculture.

tobacco smoke. There is no risk-free level of exposure to tobacco smoke pollution, which causes premature disease and death in children and adults who do not smoke. Tobacco smoke pollution causes respiratory effects in children (e.g., lower respiratory illnesses; middle ear disease, including acute and recurring otitis media and chronic middle ear effusion; cough, phlegm, wheeze, and breathlessness among school-aged children; asthma; persistent adverse effects on lung function and lower levels of lung function), low-birthweight babies, and sudden infant death syndrome (SIDS). Among adults, tobacco smoke pollution causes approximately 3000 deaths from lung cancer and 35,000 deaths from heart disease each year.[2,38] Separating smokers from nonsmokers, cleaning the air, and ventilating buildings do not eliminate nonsmokers' exposures to second-hand smoke.[38] Eliminating smoke from indoor places is the only way to fully protect nonsmokers from exposure to tobacco smoke pollution.

Overall Mortality

Counting deaths attributable to both active and involuntary smoking, approximately 39% (about 173,000) of smoking-attributable deaths (SADs) are from cardiovascular diseases, with approximately 121,900 of these due to ischemic heart disease.[2] Another 37% (about 161,500 annually) of smoking-attributable deaths are from malignant neoplasms, with approximately 126,900 due to cancers of the trachea, bronchus, or lung. Twenty-three percent (101,500) of smoking-attributable deaths are from respiratory diseases other than lung cancer (e.g., chronic airway obstruction, bronchitis, emphysema). From a different perspective, approximately 18% of cardiovascular disease deaths, 30% of malignant neoplasms, and 79% of chronic respiratory diseases in U.S.

adults are attributable to smoking or exposure to tobacco smoke pollution.

Patterns of Use

In the early 1880s the tobacco in manufactured cigarettes accounted for only 1% of all tobacco consumed in the U.S. (Figure 1). By 1950, this figure was 80%; and by 2006, 79% of tobacco consumed in the U.S. was in cigarettes.[39–41] Overall tobacco consumption peaked in the early 1950s, at about 13 pounds per person; by 2006, per capita consumption was down to 3.7 pounds per capita, the lowest estimate since recordkeeping began in 1880. Some of this decline is due to greater efficiencies over time on the part of cigarette manufacturers who make cigarettes with the stems and leaf ribs of tobacco plants and use expanded tobacco.[42,43] In addition, the addition of the filter tip has decreased the size of the tobacco column.[43] Thus, while the production of 1000 cigarettes required 2.7 pounds of tobacco in the early 1950s, only 1.5 pounds was used in 2004.[40,42] Still, the number of cigarettes consumed also has declined substantially during this time period.[44]

While overall U.S. consumption of tobacco products has been declining for several decades (Figure 1),[39,40,45,46] consumption increased from 1995 through 2006 for cigars (by 73%), snuff (by 23%), and smoking tobacco (i.e., pipe or roll-your-own) (by 15%).[40,45] From 1995 through 2006, consumption declined for cigarettes (by 31%) and chewing tobacco (by 45%).[40,45] The prevalence of cigarette smoking among U.S. adults (aged ≥18 years) declined substantially, from 42.4% in 1965 to 20.8% in 2006 (Figure 2).[47–51] Of the 45.1 million U.S. smokers in 2005, 80.8% smoked every day and 19.2% smoked on some days.[50] The decline in
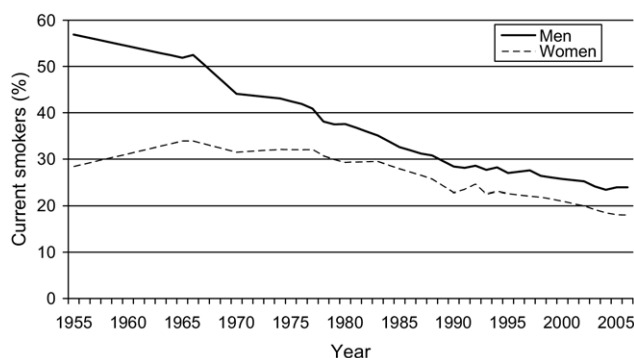

Figure 2. Trends in cigarette smoking among adults aged ≥18 years, by gender—United States, 1955–2006.[47–51] Before 1992, current smokers were defined as people who reported having smoked ≥100 cigarettes and who currently smoked. Since 1992, current smokers were defined as people who reported having smoked ≥100 cigarettes during their lifetime and who reported now smoking every day or on some days. Source: 1955 Current Population Survey; various 1965–2006 National Health Interview Surveys.

cigarette consumption in the U.S. is consistent with that of most higher-income nations.[52]

In 2005, U.S. cigarette smoking prevalence was higher for men (23.9%) than for women (18.1%); for American Indians/Alaska Natives (32.0%) than for Hispanics (16.2%) and Asians (13.3%); for those with a general equivalency diploma (GED) (43.2%) or 9–11 years of education (32.6%) than for those with an undergraduate (10.7%) or graduate (7.1%) degree; and for those living in poverty (29.9%) than for those living at or above the poverty line (20.6%).[50] Patterns of prevalence suggest that future tobacco-attributable disease increasingly will be concentrated in socially disadvantaged populations, further exacerbating health disparities. Among the estimated 42.5% (91.8 million) of people who have ever smoked at least 100 lifetime cigarettes, 50.8% (46.5 million) were former cigarette smokers. In 2005, 2.2% of adults (4.3% of men and 0.2% of women) smoked cigars; 2.3% of adults used smokeless tobacco (4.5% of men and 0.2% of women). Use of bidis and kreteks among U.S. adults is negligible. Recent data from the National Health Interview Survey (NHIS) indicate that smoking prevalence among U.S. adults leveled off at about 21% during 2004–2006.[51]

Among U.S. secondary school students, cigarette smoking prevalence increased markedly in the 1990s, peaking in 1996 for 8th and 10th graders and in 1997 for 12th graders (Figure 3) and has since declined significantly.[53] Data from 2005 and 2006 suggest that progress toward fewer student smokers is slowing and may even be stopping among younger teens.[53,54]

The 2004 National Youth Tobacco Survey collected data on current use (during the 30 days preceding the survey) of various tobacco products among middle school and high school students.[55] The prevalence of use of various products among high school students (most of whom were 14–18 years old) were: any tobacco (28.0%); cigarettes (22.3%); cigars (12.8%); smokeless tobacco (6.0%); pipes (3.1%); bidis (2.6%); and kreteks (2.3%). With the exception of pipes and
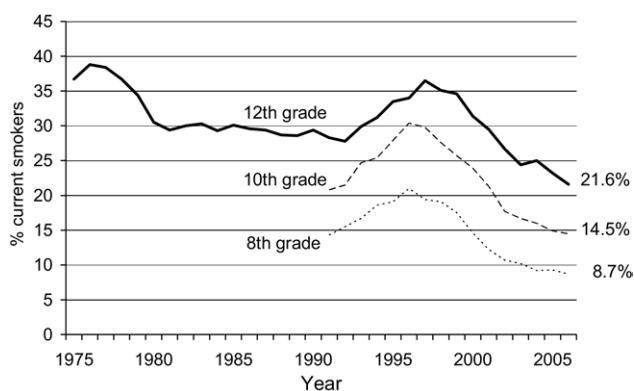

Figure 3. Trends in cigarette smoking anytime in the past 30 days by grade in school—United States, 1975–2006.[53] Source: Monitoring the Future Surveys, University of Michigan.

bidis, high school students were more likely to use each of the specific products and to use any tobacco product than were middle school students.

Factors Influencing Use

This section incorporates the traditional epidemiologic model of agent, host, vector, and environment as a framework for understanding factors influencing the development of nicotine addiction and strategies to prevent initiation, promote quitting, and protect non-smokers.[44,56] This model recognizes that factors operating at multiple levels contribute to use, addiction, disease, and death. Specifically, tobacco products are the agents of addiction and disease; smokers and users of other tobacco products are the hosts; the tobacco industry is the vector (i.e., the organism that distributes the agent); and familial, social, legal, political, economic, cultural, historic, and media influences are the environmental factors that can contribute to or prevent use.[57]

Several characteristics of the agent can influence use. For example, filter ventilation (the insertion of rings of tiny holes in filters that permit air to dilute the smoke) makes cigarettes taste lighter and milder, thus contributing to the false impression that they are less dangerous.[58,59] Ventilation also promotes compensation by allowing smokers to take larger puffs and by permitting them to block the vent holes with either their fingers or lips.[58,59] Cigarettes have been designed to allow the smoker to obtain all the nicotine he or she needs while scoring low in tar and nicotine yields on the government machine testing regimens.[13,58] Light, ultralight, and ultrasmooth cigarettes tacitly promise health benefits, but are as hazardous as full-flavor varieties.[1,13,60] Cigarette companies have made their products taste smoother and have special flavorings in response to young smokers' concerns about harsh taste.[61–64] In addition, the bioavailability and reinforcing properties of nicotine can influence use.[31,33] Research on traditional products and potential reduced-exposure products (PREPs) is needed to determine likely human exposure to nicotine and toxic/carcinogenic compounds and to better understand how tacit claims might influence use.[65]

Host factors that can influence initiation include social skills, self-efficacy, school performance/orientation, self-esteem, intentions to smoke, expectancies about smoking, other problem behaviors, and prior experimentation.[18,66–69] Biological susceptibility to nicotine addiction, in utero exposure to nicotine, and adverse childhood experiences also may play a role.[70–72] Among smokers, the number of cigarettes smoked each day and indicators of dependence are the major predictors of quitting.[73–76] Other notable predictors include self-efficacy about quitting and the duration of previous quit attempts.[73–75]

In epidemiology, the vector is the organism that transports the agent to susceptible individuals.[57] Tobacco companies market their products to maximize appeal and allay health concerns.[18,77–79] They adapted to the health concerns raised in the 1950s and 1960s with public relations strategies designed to reassure the public that cigarettes were safe, new products such as filtered and then "light" cigarettes (i.e., technologic fixes), and marketing strategies designed to communicate safety without raising concerns about health risks.[80–84] They adapted to recent restrictions imposed by the Master Settlement Agreement by focusing resources on the retail environment, bar promotions, and direct mail marketing (Chaloupka, submitted manuscript).[79,85] Companies have used pricing strategies, such as discount coupons and multipack discounts, to offset the effects of tax increases.[86] They undermine public health efforts by resisting the implementation of health-promoting programs and policies.[77,87–90] They attempt to manipulate the work of scientists studying the health effects of their products.[89,91–93]

Environmental factors include familial, social, cultural, economic, historic, political, and media-based influences. For example, smoking by peers, siblings, and parents, as well as norms established in the home, can influence uptake.[18,94] In the U.S., as well as in other countries, tobacco growing and tobacco product manufacturing have become culturally established and economically powerful enterprises that greatly influence political decisions and attitudes about use.[88–90,95–97] Other environmental factors that can influence behavior include smoke-free air laws and policies,[98,99] advice to quit from a health professional,[100,101] and media influences, such as appearances of smoking in movies, pro-tobacco advertising and promotion, and anti-tobacco messages from the public health sector.[43,79,102–104] The number of states passing smoke-free laws protecting workers in private workplaces, restaurants, and/or bars has increased recently, to 27 as of July 2007.[105] Approximately 57.5% of Americans of all ages live in areas where smoking is prohibited in private workplaces, restaurants, and/or bars.[105] Still, many workers, especially those in the hospitality industry, remain unprotected.[38,106] Laws protecting nonsmokers also can help smokers reduce consumption.[98] In addition, substantial progress has been made in reducing children's exposure in homes.[107] Well-funded tobacco-control programs are associated with reduced cigarette consumption and with lower rates of smoking among youth and adults.[108–110] In addition, the price of the product influences use, with increasing prices leading to decreased use, both by reducing the number of users and decreasing consumption among continuing users.[111] State variation in cigarette price is influenced primarily by different state cigarette excise taxes. Figure 4 shows the remarkable inverse relationship between price and consumption.
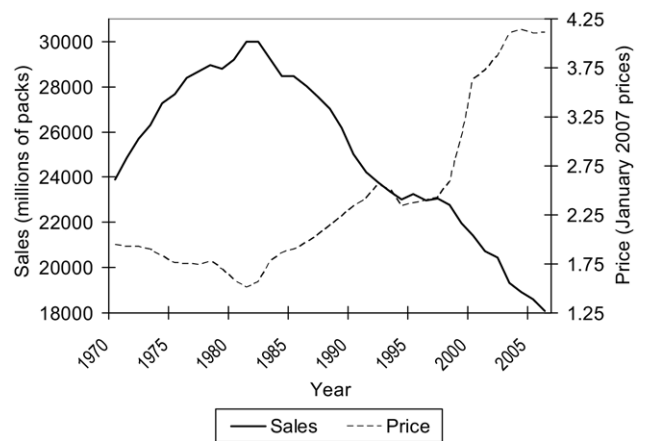

Figure 4. Total cigarette sales and cigarette prices in the United States, 1970–2006 (Chaloupka, submitted book manuscript).

Tobacco Control

Warner[104,112] estimates that the antismoking campaign in the U.S., initiated following the release of the first Surgeon General's report in 1964, has averted the premature deaths of more than 3 million Americans, each of whom has gained on average 15 years of life. This campaign is likely the most successful public health effort of the past 50 years. Numerous reports document the evidence base in support of tobacco control.[77,103,104,113] One dynamic of the tobacco-control movement in the U.S. is that some researchers and practitioners focus on individuals and others focus on policies and programs operating at the societal level. Both are important, and individual and societal factors often interact. Imagine a person who needs either to negotiate adolescence and young adulthood without becoming addicted to nicotine or someone who smokes cigarettes and is trying to stop smoking and maintain abstinence. The probability of success in either endeavor will be influenced by both individual and societal factors. For example, a young person raised on a tobacco farm in Kentucky; surrounded by parents, older siblings, and friends who smoke and who exhibits conduct problems in school would probably be more likely to start smoking than someone raised in an affluent home in California, with no smokers in his or her immediate environment, and with no conduct problems. Similarly, a smoker of 30 years who is highly addicted to nicotine and is surrounded by friends and loved ones who also are addicted to tobacco would likely have a more difficult time quitting than would someone who is only mildly dependent on nicotine and is surrounded by friends and loved ones who do not use tobacco. Individuals bring their own challenges to the task. Still, society can help, by decreasing pro-tobacco forces (e.g. tobacco company marketing) as much as possible and by (1) making cigarettes and other tobacco products more expensive; (2) decreasing the

number of places where smoking is permitted (thus reducing cues to smoke, making the effort to smoke more time-consuming, and changing the social norm); (3) providing messages in the media that motivate abstinence and educate people about how to achieve or maintain a smoke-free lifestyle; (4) increasing access to effective cessation strategies, through the provision of telephone quitlines, healthcare provider advice, and effective pharmaceutical treatments[100,114]; (5) disseminating effective prevention strategies[115]; (6) implementing effective regulation of nicotine-containing tobacco products; and (7) ensuring that the tobacco industry is held accountable for its misdeeds.

These and other policies and programs are included in the World Health Organization Framework Convention on Tobacco Control, which at the time of this writing has not been ratified by the U.S. but has been ratified by 148 other nations.[116–118] The possibility of federal legislation that would regulate the tobacco industry is also being debated in the U.S.[119–120]

The Future

The data on pounds of various tobacco products consumed per capita in the U.S. through 2004 shown in Figure 1 have been projected to depict three hypothetical scenarios in Figures 5–7, which are presented for heuristic purposes. The simple linear projection of Figure 5 suggests that work on this public health problem will be completed in about 30 years. Of course, the probability that no tobacco will be consumed in the U.S. by 2035 is infinitesimally small, for three main reasons. First, some consumers may be "hardcore," and thus unwilling or incapable of discontinuing use of one or more tobacco products. The degree to which possible "hardening" of the tobacco-consuming population influences future consumption will be influenced by the degree to which alternate reinforcing strategies and effective treatments can be identified and made attrac-
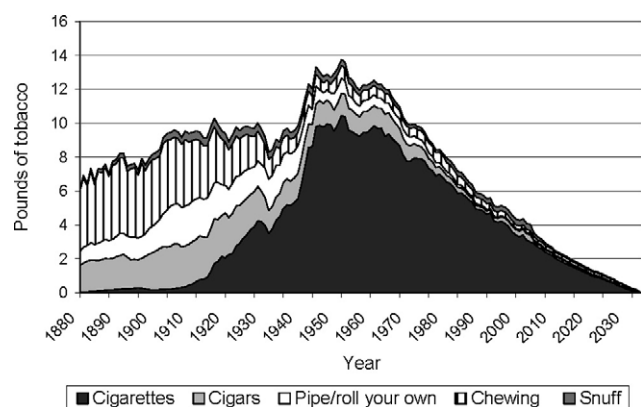
tive to consumers. Second, the tobacco industry will fight for survival, developing innovative marketing strategies of extant and new products. It will also exert its considerable political and economic influence, using lobbying and litigation to try to block effective health promotion programs and policies. Industry efforts will focus on influencing government institutions and agencies, as well as mass media outlets. Third, governments may be unwilling to forego the revenues they would lose as a result of decreased sales of tobacco products. In the short-term, lower consumption results in reduced revenues from tobacco excise taxes. In the long term, governments would pay more benefits to people for living longer. The point at which the decline begins to level off will be influenced by the relative strength of these factors.

No one really knows where and when progress will stall. Figure 6 depicts progress stalling at about 1.6 pounds per capita and more snuff being consumed
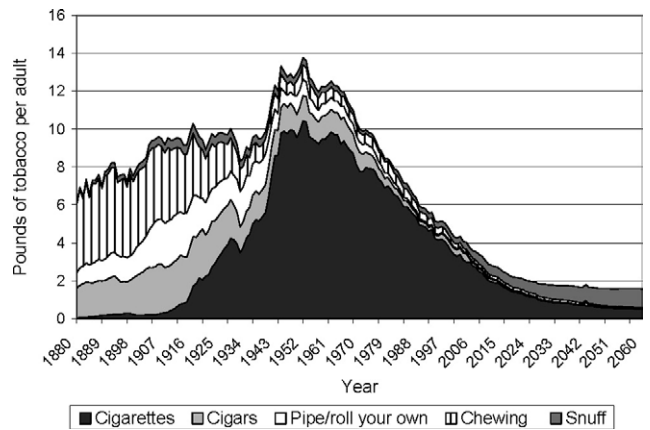

Figure 6. Trends in per capita consumption of various tobacco products—United States, 1880–2004 and possible projection to 2060.

Figure 5. Trends in per capita consumption of various tobacco products—United States, 1880–2004 and linear projection to 2035.
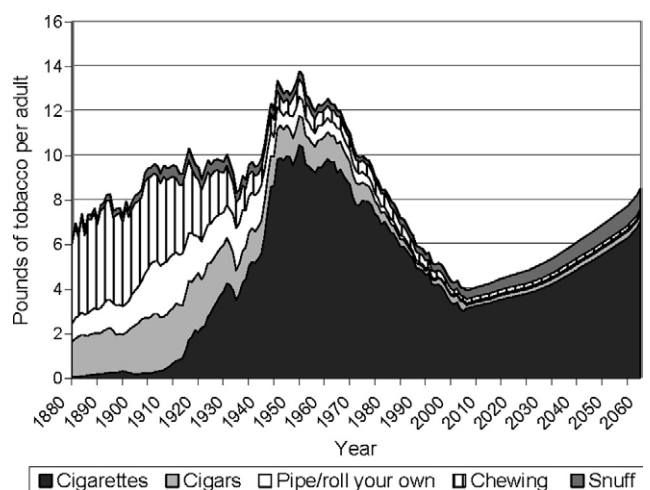

Figure 7. Trends in per capita consumption of various tobacco products—United States, 1880–2004 and extremely undesirable projection to 2060.

than cigarettes (some cigarette smokers may substitute the use of snuff to try to reduce harm without giving up tobacco). Figure 7 would eventuate if pro-tobacco forces overwhelmed health-promoting activities, a scenario that is possible, given that tobacco companies strive to maximize shareholder value. It should serve as a reminder of what could happen in the absence of vigilance and diligence on the part of those concerned with protecting public health. These and multiple other scenarios are possible.

Gray and colleagues[121] describe a long-term policy option in which cigarettes and other tobacco products are replaced by clean nicotine, defined as nicotine that is free of toxic tobacco products to an extent that would pass regulatory approval. As science advances, other scenarios (e.g., discovery of safe, attractive, and effective alternative reinforcing strategies and treatments) may also become reality. Regardless of which scenarios come into play, concerns are frequently raised about the economic impact of declining cigarette sales.[122,123] Warner and his colleagues,[123] using a macroeconomic simulation model, demonstrated that as tobacco consumption falls, employment rises in eight nontobacco regions (44 states) and drops only in the Southeast Tobacco region. Overall, there would be a gain in employment. As Warner[124] and Chaloupka (submitted book manuscript) argue, the money that is spent on tobacco does not go away. Rather, it is spent on other segments of the economy, stimulating job maintenance and creation. Warner[124] estimates that 400,000 jobs exist in the U.S. in the tobacco segment of the economy and contrasts that number with the >400,000 smoking-attributable deaths that occur annually. So 1 year of employment comes at the expense of one person losing 15 years of life from a disease caused by the product supporting the job. Because money not spent on tobacco would be spent on other goods and services, the job is replaceable. The life, however, is not.

Conclusion

This article has incorporated a holistic approach to understanding and controlling the tobacco epidemic. Continuation of the progress that has been achieved will require application of the what is already known, for as former U.S. Surgeon General David Satcher stated, "Our lack of greater progress in tobacco control is more the result of failure to implement proven strategies than it is the lack of knowledge about what to do."[77] In addition to the political will to make health-promoting policy decisions, the public also should benefit from scientific advances that help us to better prevent initiation and promote cessation of tobacco use.

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Tobacco Industry Marketing, Population-Based Tobacco Control, and Smoking Behavior

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Abstract: Two of the major influences of cigarette smoking behavior are tobacco industry marketing and public health tobacco-control activities. These vie with each other to influence the proportion of each generation who initiate smoking, the intensity level reached by smokers, and the time before smokers are able to quit successfully. This article provides a brief summary of the evidence associating tobacco marketing practices (organized under the four "Ps" of marketing), with smoking behavior. The evidence for causality in this association is considered convincing.

Publicly funded, comprehensive, statewide tobacco-control programs were introduced into the United States in the late 1980s, with money either from tobacco taxes or from legal settlements of states with the tobacco industry. These programs use organized statewide approaches to implement current recommendations on "best practices" to discourage tobacco use, recommendations that have changed over time. During the 1990s, "best practices" evolved to include protection against secondhand smoke, sale of cigarettes to minors, and restrictions on tobacco advertising. Evaluations have been published on four statewide tobacco-control programs (Sydney/Melbourne, California, Massachusetts, and Florida) and a national program aimed at youth (American Legacy Program). For each program, there was a positive association with reduced smoking. The evidence supporting the conclusion that tobacco-control programs reduce smoking behavior is evaluated as strong.
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Introduction

In 1931, Count Corti concluded his definitive history of tobacco smoking with a prediction that future efforts to curtail the spread of smoking would "result only in a miserable fiasco."[1] He based this conclusion on the history of 400 years of tobacco smoking outside of the Americas that included many fruitless attempts by powerful governments and churches to curtail this behavior. At the time of his writing, tobacco smoke was generally viewed as beneficial to health and cigarette smoking was rapidly taking over as the predominant form of tobacco consumption. During both world wars, cigarettes were provided free to solders; this resulted in a large increase in cigarette smoking.[2] In addition, from its inception in the late 1880s, the tobacco industry has used large-scale advertising campaigns to promote sales. Between 1930 and 1950, per capita cigarette consumption doubled in the United States.

However, Corti could not foresee the dramatic change that would occur 20 years later, when scientific research labeled cigarette smoking as the cause of the rapidly growing epidemic of lung cancer.[3,4] The early evidence of this link to cancer led to the first national survey on smoking in 1955.[5] At that time, only 21% of U.S. men had never smoked. Cigarette smoking was still increasing in women; approximately 50% of young adult women had smoked. Among male and female ever-smokers, only 10% were former smokers. The rate of successful quitting among regular smokers increased from approximately 0.5% per year prior to the 1950 scientific publications on the health consequences of smoking to just over 1% per year by 1955.[5]

In the U.S., public health consensus that smoking caused lung cancer was reached with the landmark Surgeon General's report in 1964.[6] This year marked the start of an ongoing tobacco-control program that has progressively evolved and strengthened over time. In 1999, the Centers for Disease Control and Prevention (CDC) summarized the evidence from demonstration programs in its publication *Best Practices for Tobacco-Control Programs.*[7]

Population Behaviors to Target Reduction of Tobacco Use

As lung cancer is a disease caused almost entirely by cigarette smoking,[2,6] the study of how smoking behavior is related to this disease provides a good focus for

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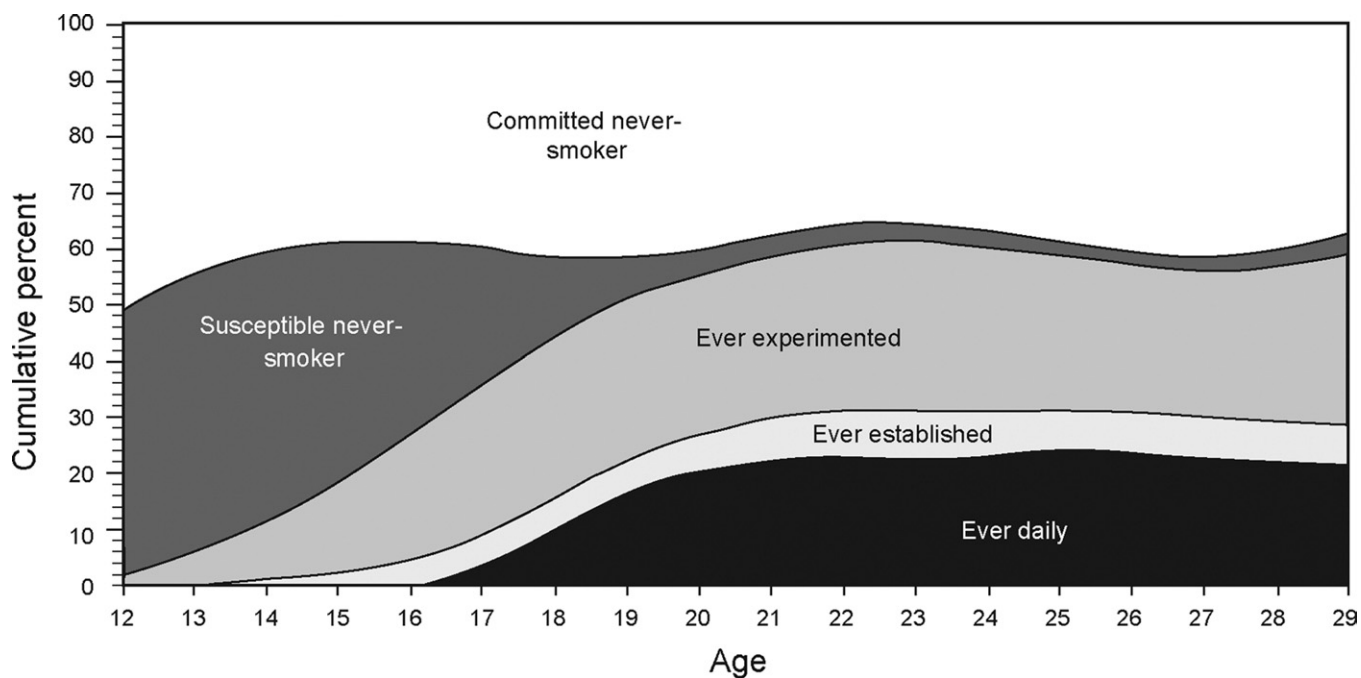
Figure 1. Smoking initiation status by age in California. 2002 California Tobacco Survey.

behaviors that should be targeted by tobacco-control campaigns. There is scientific consensus that the vast majority of lung cancer incidence can be attributed to exposure to cigarette smoke. Indeed, the best models of lung cancer indicate that rates vary with the power functions of both duration of smoking and daily consumption level.[8,9] In these models, duration of smoking is raised to the power 4 or 5, although this term also includes the variation with age, and the rates of all cancers rise rapidly through middle and older ages.[10] The number of cigarettes smoked per day is raised to the 2nd power in these models. Thus, both the duration of smoking and the intensity of smoking have a major impact on health outcomes. To minimize health consequences, public health goals need to reduce initiation, promote cessation, reduce consumption in continuing smokers, and prevent exposure to second-hand smoke in nonsmokers.

Initiation of Smoking

The first national survey of smoking behavior in the U.S. identified that most smokers started smoking regularly between the ages of 14 and 24 years.[5] However, smoking initiation is widely viewed as a process that starts with cognitions about smoking.[11] These cognitions have been combined into a measure called susceptibility to smoke,[12] which has been shown consistently to be a strong predictor of who will experiment with smoking (odds ratio [OR] consistently in the 1.7–2.2 range).[13–16] In the U.S., there is consensus that anyone who has smoked 100 cigarettes in their lifetime has established a smoking behavior.[2] Not all those who experiment go on to become established smokers. The

consensus estimate is that approximately 50% of experimenters will progress to become established smokers.

Figure 1 shows the distribution of smoking status by age for a representative sample of California adolescents and young adults in 2002. Committed never-smokers are the lowest level on this continuum and include approximately 50% of each age group from 12 through 29 years. The next largest classification for early adolescents is susceptible never-smokers. Smoking experimentation starts as young as 12 years[17] and continues until around 21 years;[18] at that age, there are few never-smokers who are susceptible to start smoking. Established smoking starts at around age 14 years and levels off in the early 20s. People who become daily smokers do so starting at around age 16 years and most appear to have achieved this level by their early 20s.

Smoking Intensity and Cessation

As previously noted, established smokers can be daily or nondaily smokers. To avoid the number bias associated with reporting in units of half-packs, daily smokers are often divided into the following three levels of intensity: light smokers, smoking less than 15 cigarettes/day; moderate smokers, smoking 15–24 cigarettes/day; and heavy smokers, smoking 25 or more cigarettes/day.[2] From 1974 through 1985, a consistent one quarter of smokers were heavy smokers.[19] There were also nondaily smokers that were former daily smokers who transition in and out of daily smoking. There is extensive evidence that in any given year, a high proportion of smokers make a quit attempt that lasts for at least a day[2]; however, the majority of these quit attempts result in relapse within a week. The probability of relapse
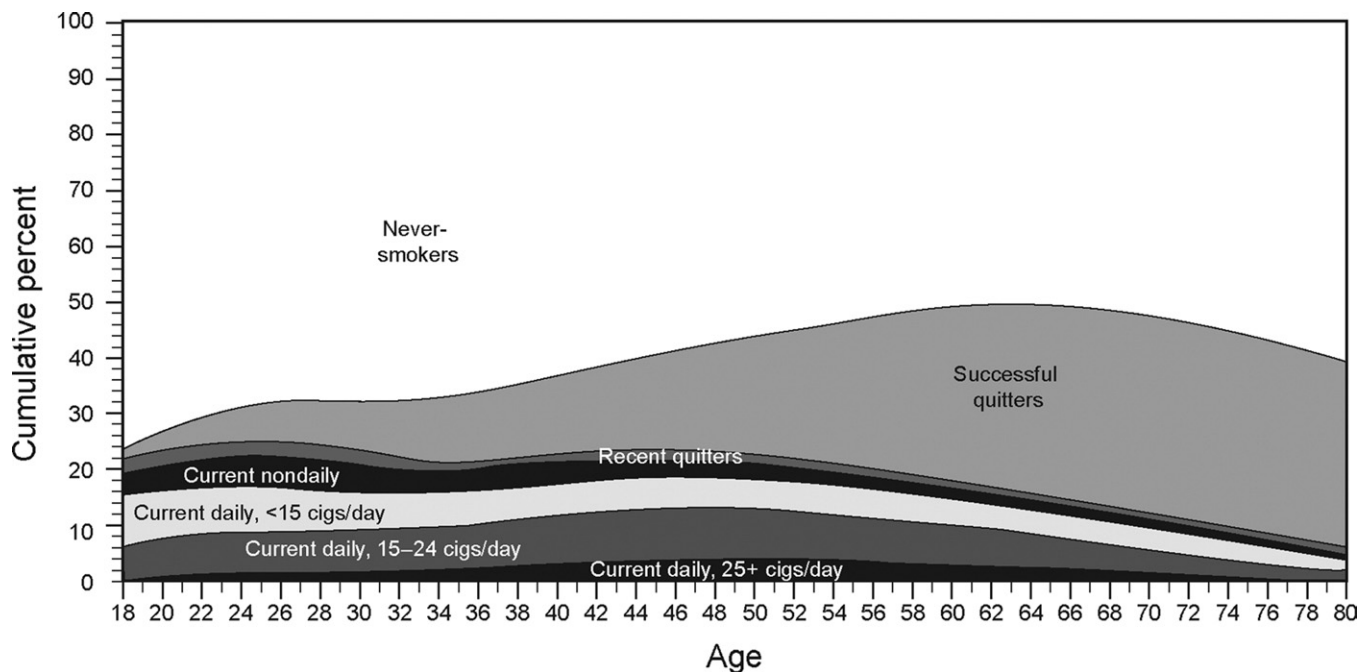
Figure 2. Age distribution of smoking intensity and smoking status from a national sample of smokers. Tobacco Use Supplements-Current Population Surveys, 2003.

does not get below 5% until the quit attempt has lasted at least 12 months, and quit attempts over this duration are labeled successful.[20]

The age distribution of this smoking intensity and quitting continuum is presented for a national sample of smokers from 2002 to 2003 (see Figure 2). Starting with people in their early 60s, each younger age group had a higher proportion classified as never-smokers (did not smoke 100 cigarettes in their lifetime). Current smokers made up approximately 20% of the population from age 18 through 50 years. The proportion of heavy smokers (>25 cigarettes/day) has declined with age and is considerably below 25% for all smokers in recent cohorts. A small and fairly consistent proportion of each age group is recent smokers (quit within past year). As smokers age, they are much more likely to become successful quitters. In this 2003 sample, approximately half of ever-smokers had successfully quit by their early 50s. The current rate of successful quitting has been estimated at 3%–4% of smokers per year, and there is little difference in this rate between younger and older smokers.[21]

The Influence of Tobacco Industry Marketing of Cigarettes

Marketing is the business of building demand for a product and is often divided into four categories: product presentation, unit price, promotion, and placement. Building product demand involves encouraging non-users to experiment and become regular users, as well as incentivizing current users not to quit or former

smokers to start using again. Cigarettes are a legal product and the U.S. has relatively few restrictions on tobacco-marketing practice.

Product Presentation

Presentation includes the size of the packet and its functioning in obtaining a cigarette, along with the colors and text on the package. Standard package size in the U.S. has been 20 cigarettes, which seems well suited to the size of pockets and purses. Providing smaller quantities for sale has been attempted in different countries. In the U.S., this has been achieved by merchants breaking open packs and selling smaller quantities of cigarettes.[22] Restrictions on product packaging have focused on requiring warning labels; in different countries, this has involved regulating the content, minimum text size, and color presentation of the warnings. The U.S. courts prohibit tobacco companies from implying health benefits through using misleading terms such as "light," "mild," or "low-tar", or through other indirect means.[23] Similar restrictions exist in Europe, Canada, Australia, and other countries, and are part of the World Health Organization (WHO) framework convention on tobacco control (FCTC).[24,25] Very limited Surgeon General warning labels on the health risks of smoking were introduced in the 1960s in the U.S.; although they have been changed twice, these minimal warning labels remain in effect. Other countries (e.g., Canada, Australia, Brazil, Thailand, Finland) have been more aggressive in replacing product advertising on the pack with counteradvertising. Starting in

December 2000, Canada required their cigarette labels to feature one of 16 full-color and sometimes graphic health warnings that cover more than 50% of the front and back of cigarette packages. A study of the effectiveness of these labels demonstrated that over half of smokers were influenced emotionally by the labels, and these smokers were more likely to quit or reduce their smoking behavior.[26] A recent multicountry survey suggests that smokers are more likely to notice such labels and to think that they are effective.[27] The WHO in its first public health treaty, the Framework Convention on Tobacco Control,[28,29] calls for large, clear health warnings that cover at least 30% of the principal display areas on the pack surfaces.

Unit Price

It is a fundamental tenet of economics that, all else being equal, higher prices lead to reduced demand. With highly addictive substances such as cigarettes, past consumption is an important determinant of consumption choices, even in the face of significant price increases. The literature has been reviewed numerous times and all of the reviews concluded that price has a major impact on smoking behavior.[30,31] Many studies, using both individual- and aggregate-level data, have estimated the price elasticity of demand for cigarettes, the percentage change in the demand from a 1% increase in price. These studies provide a very consistent estimate that cigarette price elasticity is between −0.3 and −0.5.[32] There are three separate effects associated with an increase in cigarette price: many smokers reduce their intensity of smoking, some smokers use a price increase as a cue for quitting, and there is a decline in the proportion of young people progressing to regular smoking after experimentation.

Promotion

The right to advertise tobacco products on television and in other broadcast media was removed in 1971 in the U.S. Following this ban, there was a marked decline in incidence of initiation of adolescents aged 14–17 years; this remained in effect through the mid-1980s, suggesting that restricting advertising might be effective in decreasing product use for those under the legal age to purchase cigarettes.[33] This declining trend in adolescent smoking was associated with an increasing trend in the amount of money expended on advertising and promotions by the tobacco industry.[32] There has also been a dramatic re-orientation of how the tobacco industry spends its promotional dollar. In 1990, 30% of the $3.7 billion total expenditures were on traditional advertising line items, including outdoor advertising, magazines, point-of-sale advertising, and direct mail. By 2003, this type of advertising represented only 3% of promotional expenditures. In 2005, approximately $10 billion was spent on providing price discount promotions to merchants and the annual expenditure on promoting cigarettes was approximately $60 for every adult in the country, or approximately $300 per year for every smoker in the country.[34]

These tobacco-industry, price-subsidizing promotions may have overcome the downward pressure of higher prices on initiation of regular smoking.[33] Time–series studies of innovative tobacco-industry campaigns that were established to launch products to a new demographic group also demonstrated that significant advertising in the mass media could bring new users into the smoking market; the new users were primarily between the ages of 14 and 17 years.[35,36]

Additionally, longitudinal studies have identified that these advertising campaigns appeared to work the way that theory suggested that they would. Communication theories suggest that to be effective, non-users need to be engaged with advertising messages so that they become curious about trying the product.[37] These theories argue that there should be a hierarchy of effects that target individuals receptive to the advertising message, so they are not only exposed to it, but also like the message and act on that liking. Such receptivity is correlated with smoking behavior[38] and predicts which committed never-smokers will experiment with smoking over a 3-year period,[14] as well as which committed never-smokers will be adult smokers 6 years later.[39] As envisioned by advertising theories, adolescents who are receptive to cigarette-brand advertising are also more likely to be curious about smoking, increasing the probability of experimenting with smoking.[40] Recent reviews of this literature on the effect of marketing in smoking initiation have concluded that the results of the nine published longitudinal studies are consistent in their evidence that receptivity to tobacco advertising and promotions is predictive of later smoking among nonsmokers and early-stage smokers.[41–43]

During the 1990s, the growth of this evidence on the effectiveness of tobacco marketing in encouraging adolescents to start smoking led to further restrictions on the marketing practices of the tobacco industry, as part of the negotiated Master Settlement Agreement (MSA) between tobacco companies and State Attorneys General in 1998.[44,45] Ecologic evidence of the effectiveness of these restrictions is that they coincided with a downturn in adolescent smoking following 10 consecutive years of increasing rates. This evidence is consistent in a number of surveillance data sets including the Monitoring of the Future (MTF) surveillance system, which has examined smoking behavior in a random sample of high school students every year since 1976.[46]

Placement

Placing tobacco products in movies also is a well-recognized form of marketing. The price of this advertising varies with the character who uses the product (a

hero using a product is priced highest) and whether or not use of the product helps with the plot.[47–49] Two longitudinal studies demonstrated that young adolescents whose favorite movie stars smoke on screen or who are exposed to a large number of movies portraying smokers are more likely to start smoking.[50,51] A large, national, random sample of young teens (aged 10–14 years) identified that those who were most exposed to smoking in movies were 2.6 times more likely to have started smoking than those in the lowest category of exposure.[52]

Placement of displays and advertising at the point of sale can also be considered under this heading. Cigarette pack displays have been associated with increased students' perceptions about the ease of purchasing cigarettes[53,54] and for promoting brand recall. One study suggests that point-of-sale advertising is associated with encouraging youth to try smoking.[42]

Summary

There is now considerable evidence on the association of tobacco-industry marketing and smoking behavior from many different studies using a variety of research designs. This evidence that tobacco marketing encourages smoking initation is evaluated as convincing.

The Influence of Population-Based Tobacco-Control Programs

Tobacco-control programs are coordinated community-wide programs aimed at reducing tobacco usage. Early evidence of successful community programs appeared in the 1970s, when both the North Karelia Project[55] and the Stanford Three Communities Project[56] demonstrated that a community-wide program could lead to population behavior changes. In the early 1980s, a statewide "Quit for Life" program in Sydney, Australia focused on innovative and provocative mass-media messages delivered through paid television, radio, and newspaper advertisements and was shown to effectively reduce prevalence.[57–59]

Comprehensive statewide tobacco-control programs were introduced in the U.S. in 1988, when California voters approved part of an excise tax increase to be used in a tobacco-control program.[60] The goal of the California program (1990–present) was to change the social norms surrounding tobacco, to affect all smoking behavior (adult and youth) by implementing "best practices" strategies for tobacco control, using research and development activities to improve the knowledge base for best practices. The paper describing the start of the California campaign[60] documented that best practices included: (1) increasing the price on tobacco products[61]; (2) conducting a mass media campaign[62]; (3) having appropriate school curriculum and restrictions on smoking on school grounds[63]; (4) implementing an appropriate service to assist smokers to quit both in

the physician's office,[64] in the workplace,[65] and in the community[66,67]; and (5) providing locally-based community-education activities.[68]

The following are examples of changes in best practices that have occurred after the start of the California program and demonstrate the importance of having a comprehensive program that can adjust to new developments. In 1992, the Environmental Protection Agency (EPA) classified secondhand smoke as a Group-A carcinogen.[69] Using technical support from the local programs initiative of the California statewide program, local advocates were successful in obtaining a plethora of local ordinances, which eventually led California to pass the first statewide smoke-free workplace law in the country in 1994. Additionally, smoke-free public school campuses were mandated by 1996.[70] In 1992, Congress made substance-abuse block grants from the federal government contingent on state performance in preventing minors from purchasing tobacco products. Prior to this amendment, purchase tests in many California cities demonstrated that minors could purchase tobacco over 80% of the time.[71] The final regulations on this law were published in 1996 and required statewide surveys to demonstrate achievement of a sales violation rates that did not exceed 20%.[72] The California program was one of the leaders in the nation in its aggressive enforcement practices and quickly met the standard.[72,73] Another example is the evidence that tobacco advertising and promotions encourage youth to start smoking. While the first suggestive evidence was presented in 1991, the first time-series evidence was presented in 1994, and the key evidence from cohort studies came from studies designed to help evaluate the California program.[14,39] Three major California cities (San Francisco, Los Angeles, and San Diego) had implemented ordinances restricting tobacco advertising before the MSA was enacted.[44]
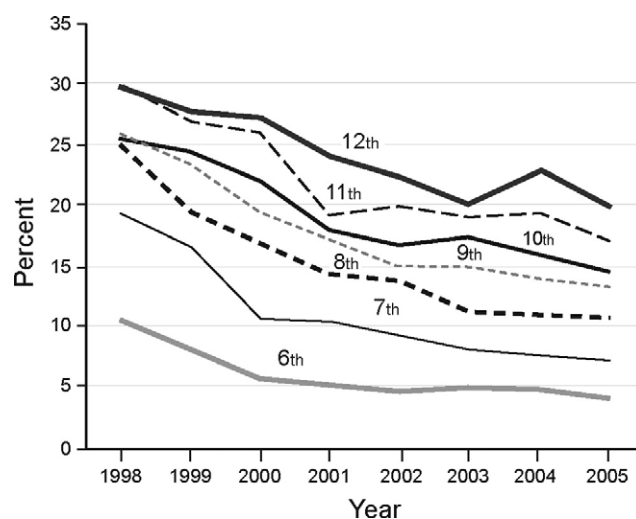

Figure 3. 30-day smoking prevalence by school grade. Youth Tobacco Survey, 1998–2005.

As the most populous state in the nation, smoking behavior in California was compared with the rest of the nation to assess the impact of the program. Using a significant pre-program period to establish baseline trends, both per capita cigarette sales and adult smoking prevalence declined as a result of the California program.[74] The program that operated throughout the 1990s has been demonstrated to significantly increase successful quitting. However, this effect was limited to adults under 35 years of age.[21] The California program also was associated with a decline in consumption among older adult smokers,[75] and with a major decline in adolescent smoking.[76]

Massachusetts was the second state to implement a large tobacco-control program in 1993, with a voter initiative directing support from a tobacco excise tax increase. Although modeled on the multicomponent California program, Massachusetts was characterized by a strong mass-media campaign and support from local boards of health and health departments.[77] Use of cigarette-sales data for evaluation of the Massachusetts program was complicated by evidence of significant out-of-state purchases because of the proximity of New Hampshire. The Massachusetts program was shown to be associated with a larger decline in prevalence than occurred in states without a program,[78,79] and the effect was seen in college students.[80] There is also evidence that the program may have reduced adolescent progression from experimentation to established smoking.[81] However, the program effect in reducing prevalence was not seen in all groups, with a lack of effect noted among women, the lower educated, and minority groups.[77] This program was similar to California (both were funded following a voter initiative process) but unlike California, this process did not require a supermajority of the legislature to remove the program. The Massachusetts program was effectively eliminated approximately 10 years after it began.[77]

A very different approach was taken by the Florida tobacco pilot program. This program was established with monies the state received from its 1997 lawsuit settlement with the tobacco industry. The program initially was managed directly from the governor's office before it was transferred to the health department and focused on youth smoking only, with input from Florida youth in planning the program focus and materials. The signature component of this program was the "Truth" multichannel media campaign that was coordinated with public events. A youth group called Students Working Against Tobacco was established and supported; in the first few years, chapters were active in all 67 counties. This campaign directly attacked the image of smoking as cool and rebellious,[32] and a downward trend in smoking behavior among youth was reported over a number of years[82,83] The most recent data are presented in Figure 3, which show a consistent decline in smoking rates within each school grade over the duration of the program. While early evidence suggested that this decline was markedly different to that observed in other states that did not have tobacco-control programs,[84] a definitive analysis of the comparative adolescent data has not yet been presented. The Florida program was discontinued in 2003.

Following the Florida lead of using settlement monies to conduct a population campaign against smoking, the American Legacy Foundation was established as part of the MSA.[85] This foundation was established in 2000 for the express purpose of conducting a national education campaign, the first national antismoking campaign in the U.S., aimed at discouraging tobacco use among youths. This campaign focused on a national media purchase that averaged $100 million per year during its first few years. The advertisements used in this campaign used graphic images aimed at exposing the death and disease caused by the manipulative marketing practices of the tobacco industry. Evaluation of this campaign used the largest and longest-running youth surveillance system for substance use, MTF.[86] This study reported that national smoking prevalence among all high school students declined from 25.3% to 18.0% between 1999 and 2002 and that the "Truth" campaign accounted for approximately 22% of this decline. While the American Legacy Foundation continues its aggressive tobacco-control program, there was a significant drop in tobacco settlement revenue in 2004 that has resulted in a smaller overall program than in the first 5 years.

In what is considered to be a major marketing initiative, Altria (parent company of Philip Morris) has created a website and materials that suggest that the company is an appropriate clearing house for all information on the health consequences of tobacco, as well as for ways to reduce tobacco use among minors. They have conducted a number of well-publicized advertising campaigns (e.g., "Think. Don't Smoke"). The tobacco industry also has provided grants-in-aid for schools to purchase the "Life skills training program," that has been evaluated as a model smoking-prevention curriculum with evidence from randomized trials that suggest it can reduce smoking.[87–89] The tobacco-industry "prevention" advertising campaigns have been demonstrated to have effects more likely to increase than decrease smoking.[88] Tobacco industry documents noted in their internal evaluation of the "Life skills" curriculum that it did not reduce smoking behavior after the second year of operation. However, this negative evaluation had no impact on the industry grant program to schools to promote the program.[90]

Summary

The evaluation of the effectiveness of tobacco-control programs to influencing cigarette smoking behavior has been compromised by a somewhat roller-coaster ride with funding. Numerous programs, funded initially with to-

bacco settlement agreement monies, were discontinued when there was a downturn in the economy. While the California program has continued to function, it has had to survive a number of attempts by different administrations to strip it of its media campaign. There also is evidence that the tobacco industry has targeted states that have tobacco-control programs with marked additional tobacco marketing efforts, an endeavor aimed at blunting the effects of the programs on smoking behavior. The overall differential in spending in 2003 was more than 25 times in favor of the tobacco industry. The evidence from studies of tobacco-control programs in Australia and California appears definitive, and studies from other states are supportive of an effect of tobacco-control program. As a whole, the evidence is evaluated as strong, although not yet convincing.

Evidence of the success of these tobacco-control programs has demonstrated that Count Corti was wrong when he concluded that attempts to introduce a smoke-free society would result in a "miserable fiasco." However, he was not wrong in indicating the strength of the opposition to these programs. The attack on the state programs has come from elected representatives, many of whom have enjoyed political contributions from the tobacco industry. In some ways, the aggressiveness of the effort to close down these tobacco-control programs is, in itself, evidence of their effectiveness.

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Policy Interventions and Surveillance As Strategies to Prevent Tobacco Use in Adolescents and Young Adults

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Abstract: Tobacco-policy interventions are designed to change the environment with the ultimate goal of preventing young people from beginning to smoke or reducing the likelihood that they will accelerate and solidify their smoking patterns. Several studies show that smoking bans in the home, at school, at work, and in the community are associated with less progression to smoking, less consolidation of experimental into regular smoking, and more quitting among adolescents and young adults. Randomized community trials and cohort studies support an association between enforcement of youth access laws against businesses and lower adolescent smoking rates. Several decades of studies provide evidence that increasing cigarette price through excise taxes reduces smoking among adolescents and young adults, who are particularly price-sensitive. Ongoing surveillance of tobacco-use behaviors in adolescents and young adults is essential for monitoring smoking patterns and evaluating tobacco policies.
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Introduction

Tobacco-policy interventions are designed to change the environment with the ultimate goal of preventing young people from beginning to smoke and reducing the likelihood that they will accelerate and solidify their smoking patterns. These strategies can increase the difficulty in obtaining cigarettes from commercial and social sources, raise the price of cigarettes, and create a normative environment where smoking is unacceptable. Policy interventions focus only indirectly on youth, but more specifically on the adults and the institutions that create the environment within which youth develop healthy or unhealthy behavior patterns. This article summarizes the evidence for the effects of clean indoor-air policies, restrictions on tobacco access, and tobacco excise taxes on reducing youth and young adult tobacco use. The need for surveillance, essential for evaluating these policies, will also be discussed. Another article in this issue discusses the related topics of mass media campaigns and advertising and marketing restrictions.[1]

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Policies to Restrict Exposure of Youth and Young Adults to Environmental Tobacco Smoke

Clean indoor-air policies are federal, state, local, and institutional policies that prohibit smoking in specified public places such as workplaces, schools, daycare centers, and healthcare facilities. While clean indoor-air policies have been in existence for more than 30 years, the number, strength, and breadth of these laws have escalated dramatically in recent years, including in such locations as bars, restaurants, and blue-collar worksites. Restaurants and bars in at least twelve countries in Europe, Africa, Asia, and Oceania are smoke-free. As of June 2007 fourteen states in the United States have adopted legislation that has or will result in 100% smoke-free workplaces, including bars and restaurants, and another seven states have 100% smoke-free bars and restaurants. In addition almost 500 U.S. cities have adopted clean indoor-air policies covering workplaces, restaurants, and/or bars that are stronger than their state laws.[2] Increasingly, organizations are adopting these policies, and 66% of households report that their homes are smoke-free.[3]

  The primary purpose of these policies is to reduce the health risks of environmental tobacco smoke (ETS) exposure, officially labeled as a toxic air contaminant by the California Environmental Protection Agency, and as a Group A (Human) Carcinogen by the National Toxicology Program of the National Institute for Environmental Health Sciences.[4,5] These adverse health effects are discussed thoroughly in the 2006 U.S. Sur-

geon General's Report. ETS exposure in children is causally associated with developmental problems such as low birth weight and sudden infant death syndrome, and with respiratory illnesses such as bronchitis and pneumonia, chronic respiratory symptoms, asthma induction and exacerbation, and middle ear infections.[3] These problems are all less likely to occur and/or relieved by reducing exposure to ETS. Some studies have found that childhood exposure to ETS increases the risk of lung cancer as an adult.[3]

In addition, growing evidence suggests that clean indoor-air policies may have a negative effect on adolescent and young adult smoking. These laws can reduce the visibility of role models who smoke, limit the opportunities for youth to smoke alone or in groups and to exchange cigarettes with other smokers, and diminish the perceived social acceptability of smoking.[6] Several studies show that smoking bans in the home, at school, at work, and in the community are associated with less progression to smoking, less consolidation of experimental into regular smoking, and more quitting among adolescents and young adults.[7–10] Restrictions on smoking where alcohol is served are likely to be especially important, given the strong association between smoking and drinking in this age group.[11] The tobacco industry has exploited this link for young adults with their extensive tobacco promotions in bars and clubs with a young adult clientele.[12]

Policies to Restrict Youth Access to Tobacco

There are two general ways that youth obtain cigarettes—through commercial sources such as stores and vending machines and through social sources such as peers, family members, or other adults. Prior to the enactment of Section 1926 (Synar Amendment) of the Public Health Service Act,[13] youth obtained cigarettes from commercial sources with relative ease.[14–18] In an examination of 13 studies conducted between 1987 and 1993, the average over-the-counter purchase success rate for minors was 67%.[15] With the hope that effectively limiting the supply of cigarettes to youth would lead to lower cigarette use, Congress mandated in the Synar Amendment[13] that all states and territories must enact laws that prohibit the sale of tobacco to minors and enforce these laws with compliance checks by underage decoys.[19]

Research has shown that sale of cigarettes to youth can be reduced through active enforcement of these Synar laws.[20–26] However, studies examining whether these policies reduce youth smoking have yielded mixed results. Several early reports found that active enforcement can reduce youth smoking;[24,27,28] other examinations have found little or no effect.[25,26,29] It is of note that most previous published studies on the effects of youth access policy were conducted in small,

isolated communities.[27] In the Monitoring the Future (MTF) survey of 8th- and 10th-grade students, the perceived availability of cigarettes began to decline in 1996 after remaining steady for years, perhaps due to the increased enforcement associated with Synar and U.S. Food and Drug Administration (FDA) regulation during this period.[30,31] One recent study of cities in Minnesota showed that youth living in communities that use compliance checks and store penalties were less likely to become smokers over time than communities that did not use such enforcement.[32] This study is especially relevant since such a large number and variety of communities were included.

Several studies have shown that restrictions on commercial access are linked to an increase in the use of social sources.[28,33] Youth who rely solely on social sources of cigarettes tend to smoke less than those who use commercial sources to get their cigarettes. Wolfson et al.[34] postulated that this is due to the fact that being a heavy smoker may be based at least partially on having the greatest access to cigarettes. In the analysis by Harrison and colleagues[35] of the 1998 Minnesota Student Survey, teens who smoked heavily were less likely to report that social sources were their only sources of cigarettes. The 1999 National Youth Tobacco Survey[36] found that 36.1% of high school regular smokers bought cigarettes in a store while only 17.0% of high school nondaily smokers bought cigarettes in a store. A recent cohort study has shown that over time young smokers who use only social sources are less likely to become heavy smokers than adolescents who use both commercial and social sources.[37]

Another tactic aimed at reducing youth access is penalizing youth for possession, use, and purchase (PUP) of tobacco. While Synar-type policies focus on reducing the supply of cigarettes to youth, PUP policies aim to stunt demand for cigarettes by introducing negative consequences that affect young smokers directly. Most tobacco-control advocates do not favor emphasizing PUP policy because they feel it reinforces the tobacco-industry messages that tobacco is for adults and implies that the individual holds sole responsibility for choosing to smoke.[38] Currently there is no strong evidence that PUP enforcement reduces youth smoking rates.[24,39] Despite this, PUP laws and enforcement of these laws have become extremely common in the U.S.[38] A recent study in Minnesota demonstrated that youth are aware of these penalties and frequently know a peer who has been caught for a PUP violation.[40] However another study showed that applying PUP penalties was not associated with a reduction in youth smoking over time, unlike applying penalties to businesses, and that cities tended to focus on one or the other strategy.[32]

Tobacco Excise Tax

Product-specific (excise) taxes, in addition to applicable sales taxes, are levied on tobacco products at the federal, state, and some local levels. The federal tax on cigarettes is currently $0.39 per pack; state excise taxes range from 7¢ (South Carolina) to $2.46 (Rhode Island) and average $1.046 per pack.[41] The range of state excise taxes reflects recent large increases enacted via statewide referenda and as a solution for recent budget shortfalls in many states. Beginning in 2002, 44 states and the District of Columbia have adopted 72 excise tax increases, averaging 43.7¢.[42] In addition, localities have added taxes, resulting in combined state–local tax rates as high as $3.66 per pack in Chicago, $3.30 in Anchorage, and $3.00 in New York City.[41] These tax increases do not necessarily translate directly into price increases, because price can be manipulated at the level of the distributor and retailer, and these practices vary by state. The best estimates of the average price of cigarettes, taking into account sales and excise taxes and variations in mark-ups and discounts, range from $3.35 per pack in South Carolina to $6.45 per pack in New Jersey.[43]

Decades of econometric research show that smokers are price-sensitive, and that increasing the price of cigarettes reduces demand. Most reports indicate that adolescents are at least as price-sensitive as adults; however, most of the studies were conducted over a narrow range of taxes considerably lower than current excise taxes. Also, youth-smoking behaviors are often less intense and habitual compared to adult smoking, and thus their responses to price potentially less predictable. The largest effects of price are seen in heavier smokers, older-aged youth, and men,[44–47] which is consistent with reports that young, experimental and female smokers obtain most of their cigarettes from social sources, and are less likely to purchase cigarettes.[36]

A series of studies using the MTF longitudinal data from 1978 to 1994 found a greater effect of price on young adult smoking than on adult or adolescent smoking. Daily, moderate, and heavy young adult smoking were all negatively correlated with the price of cigarettes, and smoking cessation and regression to lighter smoking were positively correlated.[10,47]

Additional studies are needed to examine the effects of recent large tax increases on all age groups, especially young adults, whose response to price or tax increases is largely unknown.

Tobacco Use Surveillance Systems

The primary goal of tobacco surveillance is to assess current tobacco use in a given population and to assess trends in use over time. In recent years, however, tobacco-surveillance systems have been expanded to include a variety of information that may be critical for tobacco-use prevention, including access to tobacco, perceptions and attitudes about tobacco use, media and advertising, school-based prevention programs, environmental tobacco smoke, and cessation. These data are essential for guiding research, public health programming, and public policy related to tobacco-use prevention. Current best practices for tobacco control as defined by the Centers for Disease Control and Prevention (CDC) include participation in national and state surveillance systems.[48]

National Surveillance Systems

Several surveillance systems currently exist to monitor tobacco use and tobacco-use–related information nationally. Many of these systems collect information on adolescents and young adults because the majority of prevention efforts focus on these age groups. The major national surveillance systems include the Youth Risk Behavior Surveillance System (YRBSS; 9th–12th graders), the Behavioral Risk Factor Surveillance System (BRFSS; ages 18+), the National Survey on Drug Use and Health (ages 12+), the Current Population Survey (CPS; ages 15+), and the MTF Survey (8th, 10th, 12th, and young adults). The only national surveillance system devoted solely to assessing tobacco use and related attitudes and beliefs is the National Youth Tobacco Survey.[49] This was also the first national survey to provide estimates of tobacco use for middle school students. This survey was administered in 1999, 2000, and every 2 years since then as a joint effort of the CDC and the American Legacy Foundation.

State-Leve Surveillance

State-level surveillance is also a component of a comprehensive tobacco-control program, and is critical for assessing tobacco-use–prevention needs of individual states, as well as the effects of state-level policies and programs on rates of tobacco use. The majority of states collect some state-specific tobacco-use information through the Youth Tobacco Survey sponsored by the CDC. This is a self-administered classroom survey that began in 1998 with only three states participating, and is now administered in most states with some periodicity.

Future Directions

Given the importance of surveillance for tobacco-use–prevention assessment, planning and evaluation, planning for the ongoing collection of tobacco-related information is essential. Several issues warrant consideration including the need for community-level surveillance, poor or non-existent data for specific populations, lack of measures of social and environmental factors related to tobacco use, and problems with methods for surveillance.

First, because tobacco-control efforts are primarily implemented at the state and local levels, expanding surveillance data to include prevalence rates and trends in communities is needed. Community prevalence data would be valuable to evaluate local policies and assess community-level need for tobacco prevention. These data would also allow for a better understanding of how smoking rates vary by community and examine how community-level characteristics influence smoking in those communities.

Second, expanded surveillance is warranted for specific populations that show higher rates of smoking or who are at high risk for becoming regular smokers.[50] More comprehensive data, for example, are needed on trends in smoking among young adults (individuals aged 18–24 years). This group traditionally has received less attention than adolescents because smoking initiation often begins at younger ages and it is legal for youth between the ages of 18 and 24 to smoke. Young adults, however, have the highest smoking rate of any age group,[51] and data show that young adults who did not smoke previously are becoming regular smokers during young adulthood.[52] Surveillance systems could be very valuable in understanding factors that contribute to young adult smoking and identifying effective prevention programs for this age group.

Special surveys or over-sampling should be used to gather additional data on groups disproportionately affected by smoking to provide a stronger foundation for developing effective tobacco-control programs. A consequence of representative sampling is that relatively small groups within the population are represented by small numbers. As a result, for example, the reported prevalence of tobacco use among the >85,000 American Indians in Minnesota is based on 55 individuals surveyed over 2 years as part of the BRFSS.[53] Such a number has little meaning for tobacco-use prevention or evaluation among this group when response bias and cultural distinctions are also taken into account.

More measures are needed, as part of surveillance systems, to assess how social and environmental factors affect rates of tobacco use. Historically, tobacco surveillance focused on assessing current tobacco use and monitoring trends over time, but little information has been available through surveillance systems to understand how and why changes in tobacco use occur. Understanding how social and environmental factors are related to changes in tobacco use is important for developing effective interventions that target factors most strongly related to tobacco use.

Finally, new methods for conducting tobacco surveillance may need to be considered. Currently, many surveillance systems rely on responses to telephone surveys (e.g., BRFSS). Response to telephone surveys, however, has declined in recent years, due to advances in telephone technology and cellular phone use.[54] Youth surveillance typically has been conducted in

schools, where new constraints make data collection increasingly difficult. Results may underrepresent groups who are most likely to use tobacco. Given the importance of obtaining accurate estimates of the prevalence and trends in tobacco-related information from representative samples, new methods for obtaining this information may be necessary. Research combining several possible response modes, for example combining web-based and mailed surveys, may be an effective strategy for increasing response rates and obtaining representative samples in the future.[55]

Conclusion

Research findings support the use of policy approaches to reduce youth tobacco use, including excise taxes to increase price, clean indoor-air laws, and restrictions on youth access to tobacco. These policies are part of a comprehensive tobacco-control program as outlined by the CDC, and need to be pursued at federal, state, and local levels of government, as well as in private organizations as applicable. Failure to adopt such proven strategies has been likened to withholding vaccines that are known to prevent disease. These policies and other tobacco-control strategies must be continually evaluated as well, requiring surveillance efforts that include detailed information about tobacco use and associated behaviors in all populations and all levels of organization. Programs and policies without such surveillance cannot meet the demand of accountability that is increasingly a part of government funding.

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Increasing the Demand for and Use of Effective Smoking-Cessation Treatments

Reaping the Full Health Benefits of Tobacco-Control Science and Policy Gains—In Our Lifetime

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Abstract: More adults in the United States have quit smoking than remain current smokers. But 45 million adults (20.9%) continue to smoke, with highest rates among low socioeconomic status (SES), blue-collar, and Native American populations. More than two thirds (70%) of adult smokers want to quit, and approximately 40% make a serious quit attempt each year, but only 20%–30% of quitters use an effective behavioral counseling or pharmacologic treatment. The lowest rates of treatment use are seen in the populations with the highest rates of tobacco use. Fully harvesting the last 4 decades of progress in tobacco-control science and policy to increase smokers' demand for and use of cessation treatments represents an extraordinary opportunity to extend lives and reduce healthcare costs and burden in the next 30–40 years. This paper uses the "push–pull capacity" model as a framework for illustrating strategies to achieve this goal. This model recommends: (1) improving and communicating effective treatments for wide population use; (2) building the capacity of healthcare and other systems to deliver effective treatments; and (3) boosting consumer, health plan, and insurer demand for them through policy interventions shown to motivate and support quitting (e.g., clean indoor-air laws, tobacco tax increases, expanded insurance coverage/reimbursement) and efforts to improve treatment access and appeal, especially for smokers who use them least. Innovations recommended by the National Consumer Demand Roundtable for achieving "breakthrough" improvements in cessation treatment demand and use are described.
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Introduction

Enormous progress has been made in reducing adult smoking prevalence from the time of the first Surgeon General's Report on tobacco in 1964, when almost one of two adults in the United States were smokers, to 2005, when one of five adults were smokers (20.9%).[1,2] The number of ever-smokers who have quit now exceeds the number of current smokers in the U.S., and the proportion of current smokers who are heavy smokers (>25 cigarettes/day) has declined substantially over the past decade, from 19.1% in 1993 to 12.1% in 2004.[2] In 2005, fewer cigarettes were sold in the U.S. than in any year since 1951, when the population was half its present size.[3,4] These changes are the result of four decades of comprehensive science- and policy-based tobacco control aimed at denormalizing tobacco use, preventing youth

initiation, helping addicted smokers quit, and reducing secondhand-smoke exposure.[1,2,5]

These tobacco-control advances have been hailed as one of the greatest public health achievements of the past century. However, recent annual declines in adult smoking prevalence have stalled, making it virtually certain that the *Healthy People 2010* goal of 12% adult smoking prevalence will not be reached.[1,2] An estimated 45.1 million American adults continue to smoke, with highest rates among working-class adults, those with least income and formal education, and American Indians/Native Alaskans.[2,4,6] Tobacco use remains the nation's leading cause of preventable death and disease, annually claiming 438,000 lives and accounting for $167 billion in preventable healthcare costs and lost productivity—with growing socioeconomic and racial/ethnic disparities in these health impacts.[7] Tobacco-use cessation confers substantial and immediate health and economic benefits across the lifespan, even after 50 years of smoking.[8–10] In fact, Levy et al.[8] estimate that if youth initiation were eliminated, the nation's smoking rate would change little in the near term; they project that the greatest declines in smoking-attributable death and

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disease in the U.S. over the next 30–40 years will come from adult tobacco-use cessation.

Many of the pieces are in place for substantial increases in annual cessation rates. Hard-won progress in comprehensive national, state, and local tobacco control (e.g., clean-air laws, tobacco tax increases, public education and counter-advertising, social denormalization) has moved us much closer to a world that seemed almost unimaginable 25 years ago—a world in which "nonsmoking cues and cessation information" would be "persistent and inescapable,"[11] generating unprecedented support and motivation for smokers' quitting efforts. Effective and cost-effective behavioral and pharmacologic treatments have been developed to help smokers quit and achieve long-term abstinence.[9,10] Moreover, these treatments are increasingly covered by insurers and accessible through primary care offices, provider organizations and health plans, pharmacies, telephone quitlines, and emerging online services.[12,13] Unfortunately, the hoped-for progress in national smoking and quitting rates has not occurred. While 70% of current adult smokers want to quit, only about 40% make a serious quit attempt each year, and the national annual quit rate has not changed much over the past 20 years.[2,4]

Clearly, continued progress in reducing tobacco use and increasing cessation attempts and successes among U.S. adults will require comprehensive tobacco-control polices that address both initiation and cessation and will reach all smokers. However, to reap the fullest health benefits of the impressive tobacco-control science and policy gains achieved in the past 4 decades, over the next in 4 decades, tobacco-control efforts must focus more intentionally on increasing the demand for and use of effective smoking-cessation treatments among current smokers and quitters. Today, the vast majority of U.S. smokers who try to quit still are doing so "on their own," without the benefit of treatments demonstrated to achieve quit rates substantially higher than current 5%–7% "unaided" quit rates.[9,14] In 2000, only 20%–30% of U.S. quitters reported using an evidence-based treatment, only a modest increase from the 15% reported in 1986.[15] And, disparities in treatment use continue to compound disparities in tobacco use; smokers with the least income and education, who try as often to quit as others, are the least likely to use effective treatments, and the most likely to fail when they make a serious quit attempt.[2,4,6,13] Strategies that can increase the reach, appeal, and use of effective cessation treatments hold untapped potential to reduce overall adult smoking prevalence and growing disparities in tobacco use and tobacco-caused death and disease.

To realize this potential, six leading U.S. tobacco-control funders—the American Cancer Society (ACS), American Legacy Foundation (ALF), Centers for Disease Control and Prevention (CDC), National Cancer Institute (NCI), National Institute on Drug Abuse (NIDA), and Robert Wood Johnson Foundation (RWJF)—recently joined forces to organize and fund a multidisciplinary, multisector Consumer Demand Roundtable with the aim of identifying strategies and innovations that could lead to "breakthrough improvements" in treatment demand, use, and disparities in the next 5 years (www.consumer-demand.org). The Roundtable's chief findings and recommendations will be released in a 2007 report.

This paper uses the model outlined in Figure 1, a model developed to help guide broader cancer control and health promotion research-to-practice efforts, to categorize the major challenges and opportunities addressed by the Roundtable.[14–17] It illustrates the need to work simultaneously on three fronts: (1) strengthening "science push" by proving, improving, and communicating effective treatments for wider population use; (2) building the capacity of relevant systems and institutions to deliver them; and (3) boosting demand, or market "pull," for these treatments among consumers, healthcare purchasers, and policymakers. The next sections highlight selected accomplishments and innovations in each area with the potential, when combined, to bring about substantial reductions in adult smoking prevalence and in needless tobacco-caused death, disease, and healthcare burden in the next 30–40 years.

Science Push

The science base for efforts to expand cessation-treatment use and reach is a strong one. Formal clinical practice guidelines based on over 6000 articles using well-established measures for assessing long-term effectiveness have identified efficacious and cost-effective interventions (behavioral and pharmacologic) that can be delivered at a population level in a variety of settings and modalities (e.g., healthcare, community, quitline, online), and in many cases individually tailored or targeted to the needs of priority populations.[9] Table 1 summarizes the treatments that received a grade of "A" for strength of evidence based on a consistent pattern of findings from multiple, well-designed efficacy and effectiveness trials. The odds ratios (ORs) reported in the guidelines for these treatments range from 1.3 to 2.8, with most doubling quit rates compared to unaided quitting, usual care, placebo, no medication, or other controls, and with absolute long-term quit rates ranging from 10% to 30%.[9,18]

The brief primary care intervention known as the 5A's (Ask every patient about tobacco use; Advise all smokers to quit; Assess quitting readiness; Assist those who are ready to quit with brief cessation counseling and appropriate medication and those who are not with brief motivational counseling; Arrange follow-up for continued support and intervention and more intensive treatment if needed) deserves special attention
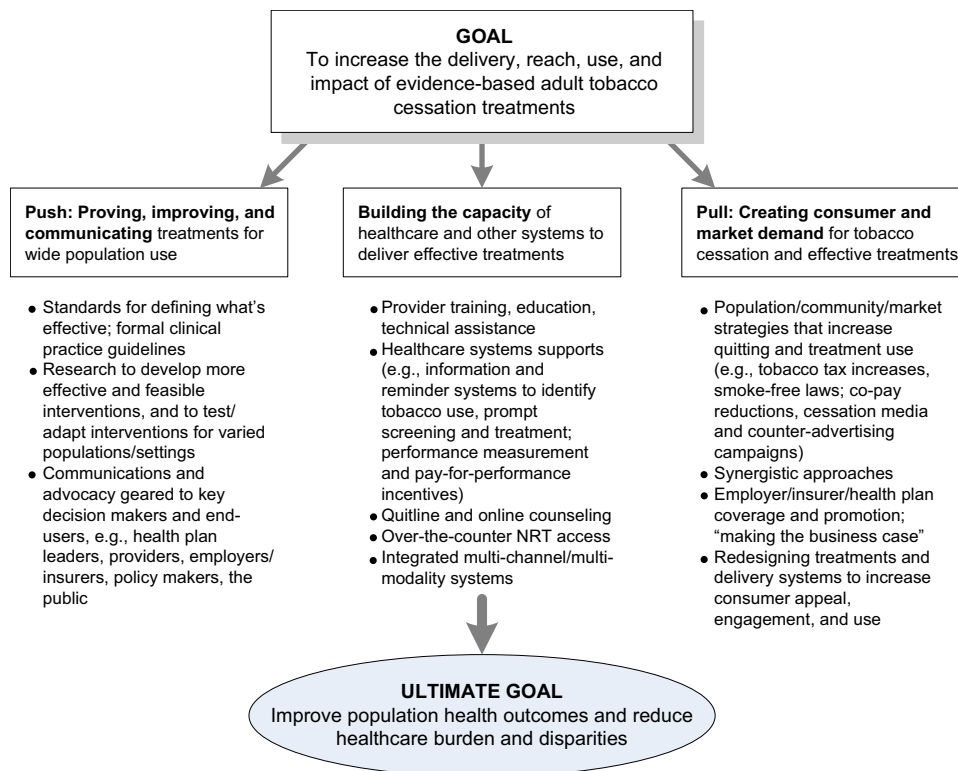
Figure 1. Increasing the use and impact of evidence-based treatments for tobacco use and dependence: science push, capacity building, and market pull.
NRT, nicotine replacement therapy.

given that 70% of smokers see their physicians each year.[9,19–21] The National Commission on Prevention Priorities recently identified the 5A's intervention as potentially the single most effective and cost effective of all clinical preventive services recommended for adults in the general population, with estimated cost savings of $500 per smoker.[19,20] Closing the gap between current rates of delivery of the 5A's and ideal rates of delivery (i.e., 90% of eligible adults) was projected to save as many quality-adjusted life years as closing the

Table 1. Treating tobacco use and dependence: U.S. PHS 2000 Clinical Practice Guideline Recommendations

Recommended treatments	Estimated odds ratio (95% CI)	Estimated abstinence rate (95% CI)
Physician advice to quit	1.3 (1.1–1.6)	10.2 (8.5–12.0)
Primary care minimal intervention (<3 minutes)	1.4 (1.1–1.8)	14.4 (11.3–17.5)
Extended counseling (>3 minutes) for pregnant smokers	2.8 (2.2–3.7)	16.8 (13.1–20.5)
Face-to-face counseling		
Group	1.3 (1.1–1.6)	13.9 (11.6–16.1)
Individual	1.7 (1.4–2.0)	16.8 (14.7–19.1)
Proactive telephone counseling	1.2 (1.1–1.4)	13.1 (11.4–14.8)
Multiple-format counseling		
2 formats	1.9 (1.6–2.2)	18.5 (15.8–21.1)
3 or 4 formats	2.5 (2.1–3.0)	23.2 (19.9–26.6)
First-line FDA-approved cessation medications		
Bupropion (Zyban, Wellbutrin)	2.1 (1.5–3.0)	30.5 (23.2–37.8)
Nicotine gum (reported for 2 mg gum only)	1.5 (1.3–1.8)	23.7 (20.6–26.7)
Nicotine inhaler	2.5 (1.7–3.6)	22.8 (16.4–29.2)
Nicotine nasal spray	2.7 (1.8–4.1)	30.5 (21.8–39.2)
Nicotine patch	1.9 (1.7–2.2)	17.7 (16.0–19.5)

Treatments not recommended: Self-help materials alone, acupuncture, hypnosis
Treatments recommended for further research: Treatments for adolescents and for smokers with mental health and/or substance abuse comorbidities; culturally-tailored treatments for racial/ethnic minority populations
Treatments not reviewed: Individually-tailored computer-based/online treatments; combined counseling plus pharmacotherapy; nicotine lozenges; varenicline (Chantix)

similar "delivery gaps" for all the other clinical preventive services recommended for adults in the general population combined (e.g., breast, colon, and cervical cancer screening, cholesterol and blood pressure screening, screening/counseling for problem drinking, influenza vaccine). Given the magnitude of its potential to improve population health, and reduce healthcare costs, burden, and disparities, the Institute of Medicine (IOM) identified this intervention as one of the top 20 priorities for all national healthcare quality improvement efforts.[21]

As Table 1 shows, the 2000 guideline panel reviewed and did not recommend self-help materials alone, acupuncture, or hypnosis. The panel did not review combined counseling/pharmacologic treatments, emerging computer-tailored and online behavioral interventions, or two newly FDA-approved efficacious medications (nicotine lozenges, varenicline), and it recommended further research for adolescent smokers and for smokers with psychiatric comorbidity and/or chemical dependency.[9,10,22] Several of these topics will be reviewed as part of the 2008 guideline update that is now underway. "A-rated" guideline treatments were recommended for wide population use, with appropriate precautions in medically high-risk groups, and with cultural tailoring for smokers in racial/ethnic minority populations.[9,23,24] The guideline update will also review new data from population-level trials, such as those recently reviewed by Cummings and Hyland,[25] exploring why increased use of over-the-counter nicotine replacement products has not influenced quit rates more substantially in the population at large (e.g., possible use by less motivated quitters and/or by non-quitters seeking short-term relief from nicotine withdrawal in smoke-free environments).

These science-based guidelines have been widely promoted to healthcare providers, health plans, policymakers, and advocates, and have furnished a powerful rationale for many healthcare practice, systems, and policy changes. These advances have included increases in: (1) the numbers of primary care providers routinely assessing tobacco-use status and advising smokers to quit, (2) the tracking and reporting provider quitting advice and assistance as core healthcare quality measures, and (3) healthcare benefits and coverage for tobacco-cessation treatments.[9,10,12–14,25,27–30] One of the chief "lessons learned" from these successes is that simply having strong scientific evidence and respected evidence-based guidelines is not enough. Strategic leadership, advocacy, and communications have been critical to translating this science base into policy and practice.[5,10,13,26,27]

These strong science-based guidelines have not, however, been widely communicated or promoted to consumers—to smokers and their families. Recent survey and focus-group data reveal wide public uncertainty about the value of these treatments, reflected in diffi-culties discriminating effective and ineffective aids and in wide misconceptions about the harms of nicotine replacement therapy (NRT) use. For instance, a 2006 RWJF national telephone survey of 1076 U.S. adults aged 18 and over (21% smokers, 47% with a high school education or less, 67% Caucasian) found limited public knowledge about effective versus ineffective treatments.[31] This survey asked which of 13 different treatments (seven evidence-based, six non-evidence-based) they believed had been "proven effective" to help smokers quit, typically doubling a quitter's chances of success.[27] While more than half rated getting help from a doctor or other healthcare professional (77%), going to a stop-smoking clinic or class (73%), and nicotine patches (58%) as effective, fewer than half placed Zyban/Wellbutrin (47%), NRTs (37%–45%), and using a telephone quitline (24%) in this category. In fact, unproven acupuncture (32%), hypnosis (39%), and quit-smoking programs offered by tobacco companies (32%) were more often endorsed as "effective" than quitlines. McMenamin et al.[32] documented similar misconceptions among Medicaid enrollees and found that the perceived effectiveness of varied tobacco-dependence treatments was significantly related to their use in this low-income population. There is growing evidence as well for public doubt and misconceptions about how over-the counter (OTC) NRT products work, with many smokers, particularly those in low socioeconomic status (SES) and racial/ethnic minority populations, concerned about their safety and addiction potential.[25,33] Bansal et al.[34] recently surveyed adult smokers and found that only 60% agreed that nicotine patches and gum improved smokers' chances of quitting, and that fewer than half believed that these products were less likely than cigarettes to cause a heart attack.

Compounding these misperceptions and uncertainties, evidence-based cessation products and services are facing growing competition from new tobacco products promoted for "harm reduction,"[35,36] from record-level tobacco industry spending ($15.15 billion/year) on cigarette advertising and promotion,[37] and from a growing proliferation of untested and unproven "miracle cures" and remedies (e.g., laser therapy, herbal remedies) exempt from U.S. Food and Drug Administration (FDA) and Federal Trade Commission (FTC) labeling and advertising regulations.[38,39] These factors combine to make effective consumer-oriented marketing and communications for evidence-based treatments more important now than ever. Direct-to-consumer marketing has been shown to help "demystify" and enhance the appeal and use of quitline services[40]; to boost the use and perceived effectiveness of NRT[41]; to generate greater treatment use when targeted specifically to underserved priority populations, including racial/ethnic minority smokers[42]; and to boost quit attempts, quit rates, and treatment use.[40–42] The intro-

duction of new medications (i.e., nicotine lozenges, varenicline)[10] and the direct-to-consumer marketing campaigns for them, and the release and promotion of 2008 U.S. Public Health Service (PHS) guideline update[28] will create new opportunities to boost the awareness, appeal, and use of treatments that work and to help smokers discriminate effective and ineffective quitting aids. They also will provide the context for innovative theory-driven studies to explore consumer treatment perceptions, expectations, and decision-making processes.

Delivery Capacity

Policymakers and healthcare, public health, and tobacco-control leaders and advocates have succeeded in greatly expanding the nation's capacity to deliver effective treatments over the past decade. Remarkable changes have occurred in the healthcare system. An increasing number of national, state, and professional groups (medicine, nursing, pharmacy, dentistry, mental health, cessation specialists) offer cessation-related training and assistance to deliver brief cessation advice and treatment.[10,12,13] Based on evidence that healthcare provider training alone is not sufficient in the absence of systems supports to increase cessation-treatment delivery,[9,43] the proportion of health plans using some system to identify smokers has risen from 15% in 1997 to 91% in 2003,[38] and the majority (over 60%) of smokers currently report physician advice to quit—advice that is associated with increased use of effective smoking-cessation treatments (counseling, medication) and with greater patient healthcare satisfaction.[12,13,19,32,44] Advances in health information technology are rapidly expanding capacity for computerized reminder systems that have been found to improve the delivery of advice, counseling and medication in 5A's primary care interventions.[11–13,28,44] There also has been considerable growth in understanding and implementing broad multicomponent healthcare systems changes to improve treatment delivery, approaches that typically combine provider training, computerized provider reminder and patient referral systems, patient self-management support programs, performance measurement, feedback, and incentives for evidence-based care.[12,13,21,26,28] The fact that tobacco-cessation advice and treatment are now metrics in the nation's leading national healthcare quality measurement systems means that pay-for-performance initiatives using these measures will bring new incentives for their delivery as part of routine primary care.[12,13]

Complementing these healthcare system changes, telephone quitlines are now available in 50 states and the District of Columbia through a single toll-free access portal (1-800-QUIT-NOW) providing smokers and providers an unprecedented barrier-free conduit to effective counseling.[10,45,46] A 2005 survey of state quitline directors found that 90% of quitlines offered materials and/or counseling in Spanish, 71% offered broader language translation services for counseling, and 35% provided free or low-cost nicotine medication to eligible adult callers, especially to low-income and uninsured smokers.[47] In addition, OTC availability of NRT gum, patches, and lozenges has widened their use, and the growth in online services hold the potential for "24/7" access to individually tailored quit smoking counseling and valuable quitting peer networking and social support.[32,48,49]

One of the most exciting possible by-products of the growth in each of these individual treatment delivery systems is the emergence of integrated multichannel, multimodality systems of care that can tailor treatment modalities and content for individuals and targeted populations, achieving higher reach, especially among low-income smokers, and possibly higher quit rates as well.[13,47,49–55] Fiore et al.,[46] Graham et al.,[49] and Abrams[50] have advocated for making the full range of cessation treatments (healthcare provider, medication, quitline, online, community-based clinics) accessible and freely available in a seamless, coordinated system of care management. For example, primary care practices increasingly are turning to telephone quitlines to provide the counseling assistance that is much less likely to be offered during brief quitting sessions by providers limited to 14-minute office visits.[13] The "Ask-Advise-Refer" campaign of the American Dental Hygienists Association and the "Ask and Act" campaign of the American Academy of Family Physicians encourage providers to conduct the first two A's of the 5A's intervention (Ask and Advise) in their offices, and to refer patients to quitlines and other external services for additional help (Assess, Assist, Arrange). In 2005, 77% of state quitlines used faxed MD referrals to facilitate such primary care–quitline linkages.[47] Under the best of these models, quitline counselors work with primary care clinicians in a team-based approach that includes follow-up collaboration.[10,13] Statewide programs in Maine, Minnesota, and New York are providing OTC NRT patches/gum to screened, eligible quitters.[51–53] In studies conducted in three states, such efforts have greatly boosted quitline call volumes, have been particularly effective in reaching and assisting low-income and minority smokers, and have improved on the quit rates achieved in the same populations with quitline-only or NRT-only interventions.[51–53] The integration of online services, particularly as the "digital divide" continues to erode, will further extend the reach, efficiencies, and social networking support of these multicomponent interventions—for both patients and providers.[48–50]

The inclusion of tobacco-use screening and treatment in the nation's leading healthcare quality improvement agendas will spur new multisystem efforts to widen the delivery of proven treatments to the smokers

who need them.[13,19–21] Public–private quitline service partnerships,[45] pharmaceutical company investments in product promotion and in individually-tailored computer-based counseling programs for FDA-approved medications,[54] and innovative minimal-contact NRT counseling and distribution strategies (such as brief pharmacist counseling in pharmacy-based health clinics serving low-income smokers)[55] are examples of promising and potentially profitable (financially sustainable) delivery systems that work around the constraints of busy primary care office practices. However, as outlined in the National Cessation Action Plan,[46] sustaining and expanding the nation's quit-smoking treatment capacity and infrastructure ultimately depends on securing needed funding from federal, state, and local tobacco-control funds, excise tax revenues, as well as original (1998) and bonus (2008) Master Settlement Agreement (MSA) funds—only a small fraction of which are currently devoted to tobacco control.[2,56]

Consumer and Market Demand

While the supply of cessation products and services has grown enormously, especially over the past decade, demand for them has not caught up, either among smokers themselves or among the public and private health plans and employers who purchase cessation products and services on their behalf. Major strides in public-policy supports for cessation and treatment use over the past decade have substantially improved national prospects for higher consumer and market demand for effective quit-smoking treatments, but further efforts are needed to reap the full benefits of these policy advances.

As outlined below, population-based public health policies recommended by the CDC to increase quitting and/or treatment use (i.e., tobacco tax increases, clean indoor-air laws, reduced out-of-pocket treatment costs, cessation media campaigns),[44] are currently reaching unprecedented numbers of smokers.

Since 1998, the combined average state and federal cigarette tax has increased from $0.59 to $1.33 per pack, with prospects for additional increases in the coming year.[56] A positive change of 10% in cigarette prices increase the probability of a quit attempt by 10%–12% and of a successful quit by 1%–2%, with greatest effects on smokers with the least income.[46,57] State tobacco tax increases not only induce quitting and deter smoking, they also hold (mostly unrealized) potential for funding comprehensive tobacco-control initiatives.

Americans for Nonsmokers' Rights reports that there are now 22 states and hundreds of additional municipalities with 100% smoke-free laws in workplaces, restaurants, and/or bars, and that 54.8% of Americans are now protected from harmful secondhand smoke in one or more of these settings.[58] These restrictions increase

population quit attempts and successes, and when coupled with treatment promotions and cost reductions, appear to increase treatment use and demand.[53,59]

In 1995, only one state Medicaid program covered tobacco-dependence treatment. In 2005, 42 state Medicaid programs and 96% of U.S. health plans provided coverage for some form of evidence-based counseling or pharmacotherapy.[30,60] Medicare now covers both counseling and medication, and the Veterans' Affairs Health Administration now covers cessation counseling.[12] Unfortunately, many, if not most, smokers eligible for these benefits are unaware they have them, making them essentially "stealth" benefits.[13,14,29,32,60]

Public health anti-tobacco advertising and cessation media campaigns and promotions have been shown to increase population quit rates, quitline calls, NRT use, and the utilization of treatment benefits.[5,11,27,32,40–42,46,61–63] However, funding for these campaigns from MSA and state tobacco excise tax revenues is only a fraction of what it could or should be.[1,2]

Demand is increased most when these public health strategies are combined. The New York City Department of Health paired a strong clean indoor-air law and recent state and local tobacco tax increases with a citywide cessation media campaign, primary care physician educational campaign, and the offer and promotion of free quitline counseling and NRT. The result was an 11% decline over 1 year in the citywide smoking rate from 2003 to 2004 (the fastest drop in U.S. smoking rates ever recorded) and a 15% decline over 2 years from 2003 to 2005, producing 200,000 new ex-smokers and averting an estimated 60,000 premature deaths.[53,59,63] Citywide mass media and neighborhood-targeted promotions offering a free 6-week supply of NRT patches to the first 35,000 eligible adult quitline callers stimulated 400,000 calls, with disproportionate response from nonwhite, foreign-born smokers in the targeted low-income neighborhoods.[53,59]

These results illustrate, at a local level, the potential synergistic effects that could be achieved nationally through the comprehensive strategies recommended by the National Cessation Action Plan (i.e., tax increases, physician training, free quitline counseling and NRT, effective treatment promotion). Replicating New York City's success at the national, state, or local levels will require proactive efforts to assure that adequate cessation resources are in place to meet the demand generated by tobacco tax increases, clean indoor-air laws, and well-publicized cessation treatment benefits. The rapid spread of clean indoor-air laws and the presence of quitlines in 50 states and the District of Columbia offer unprecedented opportunities for such planning and coordination. However, the kind of alignment achieved by New York City is rare, and limited state and local tobacco-control funding is an obstacle. The enhanced surveillance system created by the New

York City Department of Health to target and evaluate their efforts also is rare, providing much stronger epidemiologic surveillance of smokers' quitting efforts and treatment use than now exists nationally or at the state and local levels.

Boosting market demand also requires marketing efforts aimed at employers, insurers, and health plans, the nation's powerful intermediary "consumers." New evidence and tools establishing the "business case" for tobacco-dependence treatment and the inclusion of tobacco-use screening and treatment in national pay-for-performance quality metrics will be helpful, although the full return on investment is delayed by 3–5 years.[12,13,30,45] Insurers and employers also place great weight on direct employee and enrollee request, an emphasis projected to increase with the growth of consumer-directed health insurance products.[64] This places a premium on informing smokers of the cessation-treatment benefits that are available, and on discovering ways to design, package, promote, and deliver evidence-based treatments so that they are more appealing and more likely to inspire smoker demand for them as part of their basic health benefit packages.

An exciting new frontier in tobacco-cessation research and practice involves applying design principles and processes used to build demand for other consumer products to meet this challenge. The need to "design for demand" was given a high priority by the Consumer Demand Roundtable, which reached out to IDEO, a top global consumer product design firm, for help to identify possible "breakthrough innovations" in product design and delivery. The initial design principles proposed for tobacco-cessation treatments are based on: (1) IDEO's similar work redesigning other consumer products, including lifestyle and behavior-change products, to better meet their users' latent unmet needs[65]; and (2) the view that current cessation treatments and delivery systems will need to engage and support quitters all along their "quitting journeys," not just during the initial active quit attempt.[66] The following initial IDEO design principles propose strategies for building cessation product appeal, use and demand by:

(1) allowing smokers to **kick the tires** by giving them an opportunity to test or experiment with a service/product before buying into it (e.g., pharmacy-administered "trial" packages of multiple forms of NRT);
(2) **lowering the bar** to make the initial quit attempt less costly, both psychologically and financially (e.g., short-term "practice" quit attempts);
(3) **designing aesthetically pleasing products, tools, and services** that create a positive experience for consumers, especially for smokers in underserved populations;
(4) **facilitating transitions** by giving smokers appropri-ate tools and professional and social support as they move through the multiple stages of quitting;
(5) **making progress tangible** by allowing smokers to see and celebrate the small steps that are bringing them closer to their goal (e.g., cutting back before quitting);
(6) **integrating multiple often disparate treatment elements in a unified system of care** (e.g., integrated multimodality treatment and support systems);
(7) **fostering community** by linking smokers and quitters to real or virtual social support networks that prevent stigmatization and help smokers/quitters succeed; and
(8) **connecting to the rest of smokers' lives** by showing an understanding that, for many smokers, quitting is a lifestyle decision—not exclusively a health decision—that affects them in many ways and by linking them to services and supports in other arenas (e.g., exercise, weight control, appearance, and stress and mood management).

These preliminary design principles will be applied and refined through a series of pilot design projects conducted by IDEO and Roundtable members to discover innovations that will increase the appeal and use of proven cessation products, especially among the low-income and racial/ethnic minority smokers who currently use them least. While not yet formally tested, these principles are congruent with several promising innovations already in the field, including: (1) pre-quitting use of NRT to facilitate smoking cessation[67]; (2) 6-month "re-cycling" treatments for smokers who do not succeed in quitting[68]; (3) combination treatments that offer multiple medications as well as face-to-face and phone counseling over a 12-month period[69]; (4) the ALF's "Become an Ex" cessation campaign that is being designed to draw quitters and ex-smokers into an ongoing "brand community" using the same kinds of marketing techniques that the tobacco industry uses to maintain relationships with its customers[70]; and (5) programs that successfully integrate tobacco-cessation treatment into multiple-risk behavioral interventions, including diet, physical activity, and cancer screening.[71] Innovations that address smokers' obesity- and weight-related concerns may be especially appealing: Quitters in a recent study of consumer demand expressed willingness to pay more for cessation products that would help them to quit and to minimize quitting-related weight gain.[72] Innovations such as these, if found to be effective, could help guide the next generation of smoking-cessation treatment studies to discover treatments that are both effective and appealing.

An Extraordinary Opportunity

In sum, the push–pull capacity model outlines the need for efforts that: (1) strengthen and better communicate

the strong evidence for treatments that help smokers overcome tobacco use and addiction; (2) capitalize on progress in building the nation's capacity to deliver these treatments especially through multichannel, multimodality systems of care that relieve some of the burden on primary care practices; and (3) increase market and consumer demand for them by harnessing public policy changes that motivate and support smokers' quitting efforts and by designing more appealing cessation products and services. These efforts must especially target the low-SES and racial/ethnic minority populations with the highest rates of tobacco use and lowest rates of treatment use. In combination, these strategies present an extraordinary opportunity to reap the full health benefits of the past four decades of tobacco-control science and policy gains, translating these gains into longer, healthier lives and reduced healthcare costs for the 45 million American adults who continue to smoke, and addressing the nation's widening disparities in tobacco use and tobacco-caused death and disease. Combining these strategies, as demonstrated in New York City and recommended by the National Cessation Action Plan and the National Consumer Demand Roundtable, holds great promise for breakthrough reductions in tobacco use among current adult smokers and among current adolescents who do not escape future tobacco addiction. This is an opportunity that cannot be missed.

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Health System Changes to Facilitate the Delivery of Tobacco-Dependence Treatment

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Abstract: In 1996, the Agency for Health Care Policy and Research (AHCPR, now AHRQ, the Agency for Healthcare Research and Quality) released the first federal clinical practice guideline for smoking cessation that was updated in 2000 by the United States Public Health Service (USPHS). The innovative guideline identified six evidence-based strategies for healthcare systems to facilitate the institutionalization of tobacco dependence treatment so that smokers received evidence-based treatments as a routine part of health care.

A growing body of evidence demonstrates the importance of systems approaches. This paper discusses the evidence for the systems-level strategies outlined in the guidelines, as well as future directions and needed systems-level research. Promising strategies include: (1) clinical systems organized to cue assessment of smoking status and assistance to smokers, (2) leveraging clinical information systems to provide performance feedback, (3) providing full insurance coverage for evidence-based cessation treatment, and (4) including tobacco-cessation treatment as a measured standard of care by national accreditation organizations. These systems-level approaches increase the likelihood that tobacco use is addressed systematically in the healthcare delivery system. Further research to optimize the effectiveness and adoption of these strategies will help ensure that patients receive evidence-based interventions that foster tobacco-use cessation.
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Introduction

In 1996, the Agency for Health Care Policy and Research (AHCPR, now AHRQ, the Agency for Healthcare Research and Quality) released the first federal clinical practice guideline for smoking cessation.[1] Both the 1996 AHCPR guideline and its update published by the United States Public Health Service (USPHS) in 2000 were innovative in that they identified six evidence-based strategies for healthcare systems to facilitate the institutionalization of tobacco-dependence treatment.

Systems-level changes are policies and practices designed to integrate the identification of smokers and the subsequent offering and receipt of evidence-based cessation treatments into the routine delivery of health care. Systems-level changes can be direct, such as regular training of clinicians in brief cessation interventions, or indirect, such as removing cost barriers to treatment to increase use of those treatments. These strategies,[2] depicted in Table 1, are:

Implementing a tobacco-user identification system in every clinic. The goal of this strategy is to ensure that all patients are asked about tobacco use as part of every clinical encounter. Such prompts have been shown to increase the rate at which clinicians intervene with tobacco-using patients.[3–6] Such prompts also encourage clinicians to approach tobacco use as a chronic disease, requiring ongoing care similar to that offered to patients identified with hypertension or hyperlipidemia.

Providing education, resources, and feedback to promote provider intervention. The intent of this effort is to ensure that clinicians have the information and tools needed to assist their patients in making a quit attempt. Additionally, providing performance feedback also can serve as a strategy to increase rates of intervention. In essence, these strategies serve as systematic levers, prompting clinicians to take action.

Dedicating staff to provide tobacco-dependence treatment and assessing the delivery of this treatment in staff performance evaluations. Having a core staff member who takes a lead role in providing tobacco-dependence treatment to patients (or ensuring that this treatment is provided) has the potential to improve treatment delivery. This is also consistent with the team-based disease-management approach effectively applied to other chronic diseases.[7] Additionally, measuring the delivery of tobacco-dependence treatment in

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Table 1. Systems-level strategies to facilitate treatment of tobacco dependence[2]

1. Implement a tobacco-user identification system in every clinic.
2. Provide education, resources and feedback to promote provider intervention.
3. Dedicate staff to provide tobacco dependence treatment and assess the delivery of this treatment in staff performance evaluations.
4. Promote hospital policies that support and provide inpatient tobacco dependence services.
5. Include tobacco dependence treatments (both counseling and pharmacotherapy) identified as effective in this guideline as paid or covered services for all subscribers or members of health insurance packages.
6. Reimburse clinicians and specialists for delivery of effective tobacco dependence treatments and include these interventions among the defined duties of clinicians.

staff performance evaluations raises awareness of the importance of addressing tobacco use to improve health and further integrates such treatment into routine medical care.

Promoting hospital policies that support and provide tobacco-dependence services. Hospitalization is an important opportunity to intervene with smokers and address tobacco use in a more intensive manner during the inpatient stay.[8] This is particularly relevant given all hospitals in the U.S. are smoke-free and the recent Joint Commission for Accreditation of Healthcare Organizations (JCAHO) mandate to document the provision of smoking cessation counseling for patients diagnosed with certain conditions (acute myocardial infarction, congestive heart failure, community-acquired pneumonia).[9] By utilizing the hospital stay as an opportunity to offer evidence-based cessation treatment, clinicians may be able to help more hospitalized patients successfully quit using tobacco.

Including all tobacco-dependence treatments (both counseling and pharmacotherapy) identified as effective as paid or covered services for all subscribers or members of health insurance packages. Tobacco-dependence treatment is both clinically effective and cost-effective.[2,10–13] Providing coverage for tobacco-dependence treatment removes or reduces cost barriers for accessing care. Studies have indicated that cost sharing results in lower rates of utilization of evidence-based tobacco-dependence treatment[14]; strategies for reducing or eliminating these costs have the potential to increase the number of people accessing services, successfully quitting, and ultimately reducing healthcare costs.

And, reimburse clinicians for delivering effective tobacco-dependence treatments and include these interventions among the defined duties of clinicians. Clinicians frequently cite lack of reimbursement as a barrier to providing preventive care.[15] Reimbursing clinicians for

preventive care services has been shown to increase delivery of these services and improvements in health behaviors by patients, including a trend toward decreased smoking.[16]

Systems-level strategies represent a new way of thinking about treating tobacco dependence. Typically, interventions have targeted either the smoker or the clinician. In contrast, systems strategies are intended to ensure that tobacco use, the leading preventable cause of illness and death in the U.S. is systematically assessed and treated at every clinical encounter. Importantly, these strategies are designed to work synergistically with clinician- and patient-focused interventions, ultimately resulting in both activated clinicians and informed patients interacting in a seamless system that facilitates the treatment of tobacco dependence.[7] Such strategies have the potential to have a significant effect on smoking at the population level. Levy et al. estimated that a 2%–3.5% relative reduction in smoking prevalence rates could result over time from widespread implementation of such strategies.[17]

Since these recommendations were first released in 1996, new research has expanded the scientific basis for systems changes, including reviews conducted by the U.S. Preventive Services Task Force (USPSTF) on Community Preventive Services and the Cochrane Collaboration.[18–22] Manley et al. reviewed the literature on health plan implementation of both clinical and community interventions regarding tobacco use. Despite significant improvements in the implementation of systems approaches to address tobacco use by the late 1990s, opportunities for further gains remain.[23] Moreover, an evaluation conducted by the Cancer Research Network found that the adoption of health plan policies can result in the implementation of systems-level changes and increased delivery of these services to patients.[24]

In this paper, the evidence supporting systems-level approaches to address tobacco use is examined in the healthcare setting. The evidence for four of the six strategies is quite robust and is described in detail. The remaining two strategies are reported in brief as there is a less substantial evidence base for these strategies. Future opportunities for research and implementation are also discussed.

Implementation of Tobacco-User Identification Systems in the Clinic Setting

There is significant evidence that implementing a clinic-based tobacco-user identification system increases the rate of smoker identification and facilitates the provision of advice to quit and, possibly, assistance in quitting. Fiore et al.[3] conducted a prospective evaluation of expanding the vital signs to include tobacco use. Post-intervention, patients were more likely to report

being asked about smoking status, being advised to quit, and receiving specific advice on how to quit. Ahluwalia et al.[4] evaluated whether a smoking status stamp would prompt clinicians to address tobacco use among African-American patients. In this study, patients were significantly more likely to be asked about smoking (odds ratio [OR]=4.28, 95% confidence interval [CI]=3.58–5.10), advised to quit (OR=1.81, 95% CI=1.36–2.40), and have follow-up arranged (OR=2.16, 95% CI=1.30–3.38) after the intervention was implemented. Improvements were not seen in specific advice to quit nor in setting a quit date. Papers published by Chang et al.[5] and Robinson et al.[6] also noted statistically significant increases in the rates of asking and advising about tobacco use after a vital signs stamp or chart reminder system was implemented. Recent research further describes the positive impact of including tobacco use as a vital sign on rates of asking about smoking status. Piper et al.[25] studied whether the expanded vital sign stamp would increase rates of smoker identification, advice to quit, provision of assistance, and abstinence rates. Rates of asking about smoking status increased significantly. Unfortunately, rates of advice to quit, provision of assistance, and abstinence rates either were constant or decreased. Boyle and Solberg[26] evaluated whether smoking as a vital sign improved clinician cessation support in primary care and yielded mixed results. Patient self-report of advice about smoking was unchanged after the intervention. Chart documentation of tobacco use during clinical visits more than doubled (from 38% to 78%), yet documentation of advice about smoking decreased by nearly half (from 34% to 19%).

Findings from a periodic survey of health plans conducted by America's Health Insurance Plans (AHIP) show that the percentage of health plans that were able to identify either some or all members who smoke increased from 15% in 1997 to 91% in 2003.[27] Improvements in rates of clinician intervention are also seen in national data sets. Comparison of 2003, 2004, and 2005 Healthcare Effectiveness Data and Information Set (HEDIS) data collected by the National Committee for Quality Assurance (NCQA) documented modest increases in the percentage of commercial enrollees, Medicaid enrollees, and enrollees who reported receiving advice to quit smoking (current rates range from 65% to 75%).[28]

This summary indicates that implementing tobacco-user identification systems improves rates of identifying tobacco users and documenting this important information in the medical record. However, as both Piper et al.[25] and Boyle and Solberg[26] found, these systems do not by themselves consistently spur greater action by clinicians to intervene with their patients who use tobacco. Additional systems-level changes may be needed to create an environment that ensures that tobacco use is addressed in a comprehensive manner with all patients.

Provision of Education, Resources, and Feedback to Clinicians

Multicomponent interventions that incorporate both provider education and reminder systems can facilitate delivery of evidence-based tobacco-dependence treatments.[18] A review on audit and feedback in clinical practice published by the Cochrane Collaboration found that these strategies can improve provider performance, but improvements are small to modest. The effects of audit and feedback were likely to be larger when initial performance was low.[19]

Four recent studies add to the evidence base surrounding performance feedback. Swartz and colleagues[29] studied the feasibility of academic profiling, an intervention including both provider education and peer-comparison performance feedback generated from claims data and health plan data. As part of this process, the research team provided information on tobacco-related chart documentation, claims for nicotine replacement therapy and bupropion, and International Classification of Diseases (ICD)-9 coding (i.e., diagnosis coding) for tobacco use to primary care physicians. The physicians found the information understandable and indicated that it would help improve their performance, but almost half indicated that they did not believe the chart audit data accurately reflected their performance. McAfee et al.[30] evaluated the effect of automated performance feedback and senior-level incentives on provider compliance with a new system of tobacco status identification and intervention. The new system resulted in a tenfold increase in the rate of tobacco-user identification and over a threefold increase in documentation of provider advice and intervention. Middle managers reported that senior-level incentives were a powerful motivator, demonstrating a commitment to tobacco cessation among a long list of competing priorities and systems efforts. Andrews and colleagues[31] tested a multicomponent intervention to improve primary care providers' adherence to the AHCPR smoking-cessation guideline. They found that educational sessions alone had no significant impact on provider performance; however, feedback resulted in significant improvements in advice, assistance, and follow-up arrangements. Bentz et al.[32] measured the impact of practice feedback generated from electronic health record data on rates of referral to a state quitline. Rates of advice, assessment, and assistance were significantly higher in clinics receiving feedback than in control clinics. Additionally, a higher case-mix index (e.g., having a larger number of patients who were older and/or sicker than the general patient

population) and presence of a clinic champion were associated with increased rates of referral.

In sum, there is a modest but growing body of evidence indicating that provider feedback may be a promising practice for facilitating the delivery of these treatments. Additional research is needed to further evaluate how feedback should be given, what types of feedback are most effective in improving performance, and whether these findings can be replicated in other settings.

Hospital Policies that Support Inpatient Cessation Services

Hospitalization is an important opportunity to intervene with smokers and address tobacco use in a more intensive manner during the inpatient stay.[8,33] By using hospitalization as an opportunity to offer evidence-based cessation services, clinicians may be able to help more hospitalized patients successfully quit using tobacco.

There is a clear body of evidence documenting the efficacy and effectiveness of smoking-cessation interventions in the inpatient setting. A 2007 Cochrane review evaluated the effectiveness of smoking-cessation interventions for hospitalized patients and concluded that high-intensity behavioral interventions that included at least 1 month of follow-up after discharge were effective in increasing the delivery of smoking cessation treatments to inpatients compared to interventions that did not include extensive posthospitalization follow-up or that were conducted only during the inpatient stay.[21]

Systems-level changes such as policies and performance measures are critical to ensure that patient interventions are actually delivered. In 1992, JCAHO issued a standard requiring that all accredited hospitals have a policy prohibiting smoking in the hospital; by 1994, Longo et al.[34] found that more than 96% of hospitals surveyed complied with the JCAHO standard, and over 40% had enacted policies that were stricter than the JCAHO standard. In 2002, for the first time, JCAHO added performance measures for adult smoking-cessation advice and counseling for patients presenting with acute myocardial infarction (AMI), community-acquired pneumonia (CAP), and heart failure (HF) to its core performance measure set. From October 2005 to September 2006, national average rates for providing advice or counseling were 96% (AMI), 91% (HF), and 88% (CAP).[35]

The evidence is clear that hospitalization can be leveraged to help tobacco users successfully quit. Policies and performance measures, such as those adopted by JCAHO, coupled with other systems-level strategies and interventions (e.g., Smith and Taylor, 2006[36]), can help facilitate change and improve delivery of treatment in the inpatient setting.

Inclusion of Efficacious Tobacco-Dependence Treatments in Insurance Packages

Over the last 15 years, there has been a substantial increase in the coverage of tobacco-dependence treatments by publicly funded insurance programs. In 2005, Medicare began covering cessation counseling for recipients diagnosed with a tobacco-related illness, and in 2006, prescription cessation medications were covered through the Medicare Prescription Drug Act (Medicare Part D). A growing number of state Medicaid programs provide some coverage for tobacco cessation; 42 states currently cover at least one evidence-based treatment.[37] In 2006, the Veteran's Administration eliminated co-payments for cessation counseling.

Increases in coverage are also seen in the private market. A periodic survey conducted by AHIP found that health maintenance organization (HMO) plans reporting full coverage for any behavioral or pharmacotherapy increased from 75% in 1997 to 96% in 2003.[27] Findings from a 2004 survey of Wisconsin insurers indicate that 74% covered at least one pharmacotherapy and 62% covered at least one behavioral intervention.[38] However, a survey conducted by Bondi and colleagues[39] in conjunction with the Mercer Group reported that only 20% of employers included cessation coverage as part of covered benefits. As noted by Curry et al.,[37] the differences between these two studies may be due to the AHIP survey asking about the bestselling HMO product, yet most U.S. employees receive care through preferred provider organizations (PPOs). Additional research is warranted to better understand trends in coverage both by insurers and employers.

Several studies have demonstrated the use and cost effectiveness of cessation services. A study by Curry et al.[14] compared the use and cost effectiveness of three forms of coverage for smoking cessation services with a standard form of coverage. Smokers with full coverage had the highest rates of use of these services. While quit rates were lower among the group with full coverage compared to the other groups, the higher use rate resulted in more smokers who successfully quit compared to those with a cost-sharing requirement. The per member per month cost ranged from $0.07 to $0.41, depending on the nature of the coverage.[14] Other studies also found cessation services to be cost effective.[11,40,41] The Cochrane Collaboration evaluated the evidence regarding healthcare financing systems for increasing the use of tobacco-dependence treatment and concluded that offering full coverage of tobacco-dependence treatments can increase self-reported prolonged abstinence rates at relatively low costs when compared with a partial benefit or no benefit.[20]

Researchers have begun to estimate the impact of various tobacco-control policies, including cessation

treatment, on quit rates and smoking prevalence. Levy and colleagues[17,42] found that cessation treatment had the potential to increase quit rates by 5%–25% and to reduce smoking prevalence by 1%–2%, depending on the breadth of coverage, restrictions on use of such treatments, and support given to healthcare providers. While strategies such as increased excise taxes and clean-air laws were found to have a potentially greater population-wide impact, cessation treatments were noted as a key component of a comprehensive strategy that could be particularly beneficial in reaching low-income and heavy smokers.[17]

There is some evidence that full coverage of cessation treatment increases abstinence rates at a modest cost. As policy makers obtain a more robust understanding of the costs associated with tobacco use, policy changes at the federal and state level, as well as initiatives undertaken by states and insurers are helping to reduce cost barriers associated with tobacco-dependence treatment. However, challenges remain in increasing consumer demand for such treatments. Lack of consumer demand for treatment may contribute to insurers' and employers' reticence to provide barrier-free coverage. Curry et al.[14] estimated that 10% of smokers per year would utilize treatment when a full benefit was provided, as compared to 2.4% of smokers with a partial benefit. While this represented a substantial increase in utilization among people with full coverage, significant room for improvement remains.

A related issue is whether consumers are aware that their health insurance includes coverage for tobacco-dependence treatment. A study by Boyle et al.[43] found no change in the use of pharmacotherapy or long-term quit rates after implementation of a smoking cessation benefit by two health plans. However, when members were asked if they were aware of the benefit, those who were aware of the benefit were significantly more likely to use the benefit and to make quit attempts; however, long-term cessation rates did not differ significantly. The authors note that greater efforts may be required to educate smokers about the availability of covered benefits in order to see an increase in the use of these benefits.

It is also important to continue efforts to ensure that a greater percentage of employers offer these treatments as part of their basic benefits package. Ensuring that tobacco-dependence treatments are part of basic benefits packages can help reduce barriers to accessing these treatments, particularly cost barriers.

Dedicated Staff to Provide Tobacco-Dependence Treatment

A significant challenge in clinical practice is having sufficient time to completely address patient concerns and needs. An analysis of the 2004 National Ambulatory Medical Care Survey found that the median office visit lasted 14.7 minutes.[44] Conceptually, designating a tobacco-dependence treatment coordinator represents an opportunity to implement a team approach to address tobacco use and to systematize how tobacco use is addressed in the healthcare setting. There is evidence demonstrating the effectiveness of clinician intervention in increasing abstinence rates relative to self-help.[2] Additional evidence supports the use of team-based approaches for treating tobacco dependence, finding that such strategies increased the delivery of behavior change counseling in primary care.[45] Unfortunately, few health plans have implemented this strategy, nor has it been rigorously evaluated. A 2003 survey conducted by AHIP found that 16.1% of health plans reported having a full- or part-time tobacco-control staffperson, down from a high of 23.5% in 2000.[27] Given resource constraints faced by the U.S. healthcare system, it seems unlikely that this area will grow substantially, thus limiting opportunities for further implementation and evaluation of this strategy.

Inclusion of Tobacco-Dependence Treatment Among the Defined Duties of Clinicians and Reimbursing Clinicians for Providing Treatment

Few studies have evaluated the effects of financial incentives and provider reimbursement and the results are mixed.[46,47] One challenge in attempting to implement and evaluate reimbursement strategies is that few clinicians are aware of a patient's insurance coverage and whether the patient's insurance will reimburse them for providing cessation treatment. As reported by Taylor and Curry,[47] this lack of information "highlights the importance of uniformity in providing reimbursement across the multiple plans with which providers can contract."

The Medicare program represents an opportunity for further study of this strategy. In 2005, Medicare Part B coverage was expanded and clinicians can be reimbursed for providing intermediate-level or intensive cessation-counseling services. Theoretically, this addresses the issue of uniformity in providing reimbursement raised by Taylor and Curry[48] for this population. It will be important to monitor the use of these reimbursement codes as well as use of the Medicare pharmacotherapy benefit to see whether this payment strategy increases the provision of cessation counseling services.

Future Directions

Systems changes have the potential to increase rates of tobacco-user identification and intervention, and

subsequently to improve the health of patients by facilitating quit attempts. A growing body of evidence demonstrates the promise of systems approaches and institutionalization of these approaches is essential to their long-term success. Performance measurement, via measures adopted by HEDIS and JCAHO, and evaluation are essential to allow systems to be recognized for areas in which they are doing well or have made improvements, as well as areas requiring additional attention.

Implementation of systems-level changes is not solely the purview of primary care and hospital settings. Improving the delivery of tobacco-cessation interventions in health systems that serve socioeconomically disadvantaged populations is particularly important, given their high rates of smoking.[49] There is encouraging evidence that health system strategies work in settings like federally qualified health centers.[50] Moreover, healthcare settings and professions, including dental practices and pharmacies also can effectively implement such strategies.[51,52] Additional evaluation and dissemination of best practices is essential to facilitate the continued implementation of such strategies throughout the healthcare delivery system.

Despite the tremendous progress in this field over the past 15 years, further work is needed to ensure that all tobacco users are identified and are offered evidence-based treatment for tobacco dependence each time they present to the healthcare system. This goal is particularly salient given that tobacco use is responsible for approximately one third of cancer deaths and approximately 18% of all deaths in the U.S. annually.[53–57] Further, since over 70% of smokers visit a primary care physician each year,[58] the healthcare delivery system increasingly must address tobacco dependence and implement evidence-based practices to facilitate delivery of such care. Manley et al.[23] called for health plans to become more actively involved in tobacco control and proposed a model—the 5C's (covering, counseling, capitalizing, collaborating, and counting) to facilitate their involvement.

In addition to the model proposed by Manley et al.,[23] several authors have identified key healthcare-systems research questions to better understand how to foster the routine assessment and addressing of tobacco use and dependence.[18,48] Health services researchers and funders may wish to target some or all of these questions.

- Systems approaches such as tobacco-user identification are successful in improving documentation of patients' tobacco use, but do not necessarily result in further intervention. What strategies can be implemented and evaluated to foster provision of quit assistance and follow-up for patients who smoke?

- What are the most and least effective combinations of services in multicomponent interventions?
- How can population-based treatments such as quit-lines or web-based cessation services be integrated into clinical systems?
- How effective are the HEDIS and JCAHO measures in improving patient receipt of evidence-based treatment for smoking cessation and patient tobacco use cessation?
- What would be the impact of a JCAHO requirement mandating that tobacco use be addressed for all hospital admissions?
- How does the base rate of tobacco use in a managed care organization or insurance plan affect implementation of systems-level changes and outcomes?
- How can different types of tobacco-cessation interventions be most effectively integrated in managed care organizations?
- What are the costs, cost-benefit, and return on investment of system-level interventions?
- How can technologies such as patient registries and electronic medical records be used to facilitate delivery of evidence-based tobacco-dependence treatment?

Systems changes hold great promise and offer significant opportunities for addressing tobacco use in the healthcare delivery system. It is incumbent on all of us—researchers, policy makers, healthcare systems leaders, healthcare professionals, and advocates—to continue and expand efforts to ensure that tobacco use is addressed systematically throughout the healthcare delivery system. It is also our responsibility to continue to evaluate such strategies and share lessons learned and promising practices, to allow all patients—regardless of the type of healthcare delivery system they encounter—to receive evidence-based interventions that foster tobacco-use cessation.

Sanofi-Aventis or Pfizer for scientific consultation and/or scientific presentations.

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Quitlines
A Tool for Research and Dissemination of Evidence-Based Cessation Practices

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Abstract: Quitlines in the United States have grown dramatically over the past 15 years, from one state and a handful of health plans to all 50 states and over 200 health plans and employers. Over half a million tobacco users received help from state quitlines alone in 2005. Research to confirm and improve quitline effectiveness also has burgeoned, with multiple meta-analyses confirming a dose-related treatment effect. Quitlines are increasing the depth and breadth of services offered, including the integration of medication support and other electronic communication mediums such as web and e-mail.

Quitlines have the capacity to serve a larger fraction of the population than they currently serve. Accomplishing this is dependent on creating ambitious, multi-institution funding and delivery mechanisms, as well as further research and development to improve reach, effectiveness, and efficiency.
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Background

Despite decades of research and dissemination effort, use of evidence-based counseling support by those trying to quit smoking is infrequent. Only around 1% of smokers trying to quit report receiving any behavioral assistance beyond static printed materials.[1] One bright spot in this otherwise grim picture is the recent marked increase in the availability and use of a new medium for receiving behavioral support: the telephone.

In 1992, California had the only state-level quitline in the United States, with just a handful of health plan quitlines. By 2006, there were quitlines in all 50 states, all ten Canadian provinces, and 30 other countries, as well as over 200 employer and health plan quitlines. That year over half a million people received services from the U.S. state quitlines alone.[2] What explains this relatively rapid dissemination, and what lies ahead?

Quitlines provide a broad range of cessation-support services, primarily via the telephone. Services range from a single brief reactive coaching session provided at the time a caller reaches the quitline, to in-depth counseling via multiple proactive follow-up calls originating from the service provider, with pharmacotherapy mailed directly to the caller's home. Most counseling is provided by paraprofessionals following a semi-structured protocol giving practical advice, encouragement, and assistance based on the evidence-based findings of the U.S. Public Health Services (USPHS) Clinical Practice Guideline.[3] For example, callers are encouraged to set a quit date, remove smoking paraphernalia from their home and car, strive for total abstinence, and anticipate future triggers or challenges. They may receive problem-solving and skills training based on reviews of past quit attempts. In their provision of social support, phone counselors often blend elements of several counseling theories and approaches (i.e., Cognitive–Behavioral Therapy,[4] Stages of Change,[5] Motivational Interviewing,[6] Solution-Focused Therapy[7]). Increasingly, cessation medication is being integrated into service provision,[8,9] ranging from screening and decision support to fulfillment via mail order or pharmacy vouchers.[10] Quitlines often provide brief coaching to proxy callers such as friends and relatives as well as healthcare providers. They also provide callers with cessation materials and referral to local resources.

Quitlines are a robust and promising venue for the rapid pursuit of practical behavioral and translational pharmacologic research. The large number of tobacco users receiving services based on centralized computer-driven protocols provides numerous opportunities to conduct large randomized and quasi-experimental trials. The 2006 Cochrane Review found 48 phone-based cessation studies meeting its strict criteria for evidence review, examining outcomes for 36,000 callers.[11] Numerous opportunities also exist to analyze results of natural experiments growing out of variations in service-provision policies in different settings and over time.

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This article reviews the evidence base and benefits of quitlines, as well as how services are delivered and promoted. The evolving role of public–private partnerships is examined, followed by an exploration of five policy and implementation challenges quitlines face in the future. Ten opportunities for development and research are then presented, focusing primarily on the U.S.

Evidence Summary

A strong evidence base supports quitline efficacy and effectiveness.[12,13] The 2006 Cochrane Review found a 1.41 odds ratio (OR) (95% confidence interval [CI]= 1.27–1.57) for long-term cessation for people receiving phone counseling compared to people trying to quit without counseling assistance.[11] A meta-regression detected a significant association between the maximum number of planned calls and effect size. The Cochrane Review concluded that: "Proactive telephone counseling helps smokers interested in quitting. There is evidence of a dose response; one or two brief calls are less likely to provide a measurable benefit. Three or more calls increase the odds of quitting compared to a minimal intervention such as providing standard self-help materials, brief advice, or compared to pharmacotherapy alone. Telephone quitlines provide an important route of access to support for smokers, and callback counseling enhances their usefulness." Similar findings and conclusions resulted from earlier meta-analyses[14] including ones conducted by the U.S. Preventive Services Task Force,[15] the USPHS Clinical Practice Guideline,[3] and the U.S. Community Preventive Services Task Force.[16]

The cost effectiveness of cessation treatment in general is well-established, with actual positive return on investment in worksite settings[17] and one of the best cost-effectiveness ratios for any preventive or healthcare intervention from a healthcare[18,19] perspective. Quitlines generally have similar costs and deliver similar quit effects as in-person interventions. A number of cost-effectiveness analyses have looked specifically at quitlines and have found them to be highly cost effective compared to most other healthcare or preventive interventions, even for modest increases in quit rates, with incremental costs to achieve a quit in the several thousand dollar or less range.[20–23]

The interrelationship between the benefits of medication and the benefits of phone coaching is an area of some controversy. Most drug trials have embedded large doses of behavioral counseling (e.g., 25 brief sessions in Phase III varenicline trials[24,25]), but most people using the medications in the real world do so without any counseling. Some insurance companies and states have strongly encouraged and even required quitters using medications also to receive some counseling, hoping to maximize quit success. Others have argued against this approach, concerned that it will decrease use of medications, although there is no evidence to support this decrease for phone counseling.[26] There has also been some concern as to how much additional benefit is added by providing counseling for those using medications. In four large trials, Swan,[10] Zhu,[12] Hollis,[22] and McLeod[27] all found that repeated phone counseling increased the long-term effectiveness of cessation medications, although three much smaller studies (one had less than 40 phone users/cell) found no benefit.[26,28,29]

Data on the demographics and smoking characteristics of quitline callers are collected at the state level, but have not yet been collated nationally. The California Smoker's Helpline found that compared to users of other forms of cessation assistance, callers to quitlines tended to be younger, more evenly divided between men and women, and more racially and ethnically diverse, with African Americans calling the quitline at twice the expected rate.[30,31] The New Zealand Quitline found a 67% increase from 2001 to 2005 in the number of under-25 smokers and a doubling in pregnant women callers.[32] Many quitlines provide special services to those who are uninsured and on Medicaid, and these groups are often overrepresented in quitline callers.[33]

Benefits of Quitlines

Quitlines help increase the reach of evidence-based services by increasing convenience and anonymity, and by providing multilingual services. They provide extended hours of operation and centralized quality control, and eliminate transportation barriers more easily than many face-to-face cessation services. They can help people gain access to pharmacotherapy as well as the behavioral and adherence support that maximize medication effectiveness. Quitlines provide a centralized triage point for all cessation services in a region. They can enhance population quit rates in clinical practices (e.g., from 4.1% to 13%[34]), worksites, and geographic regions. This may be accomplished by direct effects for those calling, as well as by secondary effects such as inspiring quit attempts in noncallers exposed to promotion,[35] enabling clinicians to intervene more routinely with smokers, and encouraging legislators to continue funding multicomponent tobacco-control programs.

How Quitline Services Are Delivered and Financed

There is wide variation in the U.S. in the populations that quitlines serve, who delivers the services, and how they are financed. Quitlines have been set up to deliver services to all residents in some municipalities and counties, and in all states. Some limited services for special populations, such as pregnant women, have been provided at the national level. Quitlines also may

provide services to health plan members, employees, or union members. Services are delivered by a wide variety of providers, including academic and healthcare institutions, governmental and philanthropic organizations, as well as private companies, including wellness and disease management.

Financing for quitline services varies significantly including: (1) state funding from tobacco taxes, Master Settlement, and general funds; (2) health plans through benefit coverage or administrative services; (3) employer coverage as a health or wellness "carveout"; (4) Federal funding to support state services and a single-number national triage function; (5) philanthropic support underwriting indirect service costs, serving special populations and promotions; and (6) financing for the development and research base for quitlines that have come from eclectic sources, including the National Institutes of Health (NIH) and other federal agencies, philanthropic organizations, state health departments, private investors, and healthcare systems.

Elements of service also can vary widely (see Table 1). Based on evidence that end-user payment markedly decreases use,[21] very few quitlines charge users for service. States are spending over $40 million/year on service provision (based on state self-report survey data showing a mean of $828,000/year), which represents about 7% of their tobacco-control budgets (see Table 2).

How Quitlines Promote Services

A broad range of marketing techniques has been used to generate calls to quitlines. State-level quitlines initially relied primarily on mass media ads, especially television. This medium has proven reliable for call generation, but is quite expensive per call generated, sometimes requiring as much investment to generate a call as is spent on providing service for the caller. In addition, the promotional effect tends to be short-lived, tailing off after a few days or weeks. However, many state health departments believe that there are ancillary benefits to these mass media promotional campaigns, including exposure to important public health messages and increased quit attempts in the population.

Table 1. Quitline service delivery mechanisms

Who delivers	What is delivered
• States	• Reactive coaching
• Federal agencies	• Materials fulfillment
• Health plans	• Proactive coaching
• Employers	• Community referrals
• Philanthropies	• Interactive recorded messages
• Health systems	• Provider referrals
• Stand-alone companies	• Nicotine replacement therapy
• Universities	• Bupropion and varenicline decision support
• Disease management	• Integrated Web services

Table 2. Budget and utilization for state-level quitlines, July 2004 to June 2005 ($)

	Quitline service (n=44)	Quitline promotion (n=32)	Tobacco control (n=43)
Range	40K–4.2M	20K–5.5M	280K–93.4M
Mean	828K	817K	12.6M
Median	622K	206K	6.1M

Note: Live calls to all quitlines numbered approximately 500,000 during the year.
Source: North American Quitline Consortium Survey.

Other common forms of promotion by state quitlines include: (1) outreach to health plans, hospitals, and medical groups; (2) outreach to local health department personnel and community organizations; (3) enhancement of "viral" marketing to encourage peer referrals, such as including pocket cards with the quitline number in materials sent to callers; (4) use of brief courses of nicotine replacement as an inducement to call, relying on earned media and word of mouth; and (5) inclusion of quitline information in targeted mailings, such as to Medicaid recipients. Many mature state quitlines have seen a shift in the mix of caller referral source over time, with a larger fraction made up of referrals from friends, family, and healthcare providers.

Public–Private Partnerships

There are increasingly sophisticated public–private partnerships extending the depth and breadth of services offered. Integration often occurs at the state level, with another layer at the national level. As of July 1, 2006, every state in the U.S. has some form of operational quitline. The National Cancer Institute (NCI) and the Centers for Disease Prevention and Control (CDC) have collaborated with states to create a formal national network of quitlines, with a single number (1–800–QUITNOW) available as a portal that automatically routes calls back to their respective state quitlines. There is not yet funding to support an ongoing paid national promotional campaign, although a public service announcement campaign is being developed to be made available by NCI in 2007.

Some states such as New York, Minnesota, Ohio, Oregon, Utah, and Washington are collaborating further with health plans and businesses that provide and/or fund in-depth telephonic coaching services and full pharmacotherapy. In these states, callers to the state quitline who have private health plan or employer-based cessation phone and pharmacotherapy benefits are triaged via a "warm transfer." The caller stays on the line while the state operator connects them directly to the quitline service provider for the health plan or employer, with the operator staying on the line to confirm connection. These state lines thereby conserve limited government resources and thus can provide more full proactive service and

pharmacotherapy for those without alternate funding sources, such as the uninsured. Other states such as Massachusetts are providing state-supported proactive phone counseling services to health plan members if the health plans provide full pharmacotherapy. States that do not have these types of relationships frequently have to cut back on quitline promotion to ensure they have sufficient funds to provide services to callers or provide lesser service to some callers (such as a single call) as demand outstrips funding.

These ambitious, complex partnerships have been fostered by the creation of a North American Quitline Consortium (NAQC).[36] NAQC was initially supported through funding from the American Legacy Foundation (ALF) and is now incorporated as a separate nonprofit corporation with multiple funding sources. NAQC includes Federal agencies such as NCI and CDC, state health departments, state-level foundations set up to administer tobacco settlement funds, cessation-service providers, and researchers. Analogous Canadian institutions and researchers have been members since NAQC's inception, and Mexico will likely join in 2007. NAQC has provided a forum linking those involved in researching, overseeing, and operating quitlines, and conducts a yearly survey of all quitlines in North America and Europe.[37]

A limitation affecting public–private partnership efforts in the U.S. has been the heterogeneity of services, promotion, and funding at the state level, as some states provide only limited services, (i.e., a single call, with minimal promotion) while other states provide robust promotion and services (either through direct provision such as in Maine, or via public–private partnerships as described above). Call rates range from less than 1% of smokers/year to over 8%[38] at the state level. Australia and the United Kingdom, during periods of more marketing and service funding, have averaged 4%–6%.[39,40] Some employer-phone programs have reached into the 20% level, when combined with incentives such as healthcare premium differentials and smoke-free campuses.[41]

The heterogeneity of state funding has led to challenges implementing a national-level promotional campaign since many states do not have funds budgeted to handle increased demand. In 2006 and 2007, ALF is running mass media campaign pilots in four metropolitan areas that will include promotion of the 1–800–QUITNOW number. If successful, the pilot will be followed by a national media campaign, funded jointly by ALF and states.

Five Policy and Implementation Challenges for the Future
1. Under-utilization

The biggest current challenge for quitlines is that despite dramatic growth over the past decade, they are under-utilized compared to their potential. This under-utilization is in part related to decisions by sponsoring organizations not to maximize participation, due to lack of sufficient funding to support both promotion and service provision.

The National Action Plan,[42] created by the Subcommittee on Cessation of the Interagency Committee on Smoking and Health, convened by former U.S. Department of Health and Human Services (USDHHS) secretary Tommy Thompson, predicted that with unfettered access to proactive telephone counseling and pharmacotherapy coupled with robust promotion, at least 10% of smokers/year would use phone services nationally, with a 20% quit rate. This is a fivefold to tenfold increase over current use rates. From experience to date, this number appears ambitious, but achievable with markedly improved funding and sufficient infrastructure development. The Plan called for funding from a national cigarette tax to create a delivery and promotion infrastructure capable of actually reaching this level of promotion and use. It estimated that such an initiative could result in one million smokers quitting per year. Although there was support for the concept of such a bold societal intervention, there has not been funding support at the federal level beyond $25 million by the NCI and CDC to support the 1–800–QUITNOW infrastructure and to create initial capacity in states without a quitline. Therefore, a critical challenge at this point is the further evolution of existing services and the creation of a mechanism to actually fund, promote, and deliver these services at a level that creates a more significant public health impact.

2. Who Funds and Delivers Services?

Initiatives begun at higher levels to fund and deliver quitline services run the risk of undercutting motivation for local or parallel efforts. For example, before the implementation of the National Network of Quitlines concept, several state legislatures opted to not fund state quitline activity and rather to rely on an NCI-funded "free" quitline service. Some regional health plans have decided to not cover phone and pharmacotherapy for their smokers as long as they can refer them to their state quitlines. If the higher-level services are robustly funded for service provision and promotion, these negative consequences may not outweigh the benefits of more uniform service access. However, the current reality is that services and promotion are diffusely underfunded. Having any institutional player opt-out decreases the fraction of smokers who receive services. This is particularly unfortunate if a lower-level or lateral potential funder is more motivated to achieve higher utilization rates. For example, employers stand to gain when an employee quits smok-

ing from both healthcare utilization decreases and improved productivity.[43]

In addition, there are certain quitline functions that may be more achievable at specific institutional levels or when delivered by specific entities. For example, coordinating referrals to local resources and integrating a quitline into local tobacco-control campaigns may be more practical when delivered at a state level. Leveraging quitline availability to increase healthcare provider compliance with quality guidelines[3] that encourage clinician identification and intervention with tobacco users may be more achievable with a health plan-administered quitline. Employers can provide participation incentives that are impractical at the state level.

In the absence of a dramatic breakthrough at the national level, such as a dedicated increase in the cigarette tax or a favorable ruling or settlement in the appeal of the Department of Justice case suing the tobacco industry, one can probably expect only evolution, not revolution, in funding support.

3. Creating Demand for Services

There is a related challenge to discover more effective and efficient means of creating demand for quitline services. Surveys indicate that most smokers are either unaware of the existence of quitlines[44] or, if they are aware, have little idea what type of service is available. Some fear they will be lectured if they call. Promotion campaigns that demystify and normalize getting help from a quitline are in the planning stages.

There is one straightforward policy solution to markedly increase demand that has been tested in several other countries, including Australia, Brazil, parts of the United Kingdom, and the Netherlands[45] requiring tobacco companies to place a national quitline number on all cigarette packs. This strategy has resulted in dramatic increases in call volumes at no promotional cost. For example, Brazil requires that tobacco companies print the national quitline number on every cigarette pack with large graphics, resulting in enormous call volumes (averaging over 2 million/year, more than the rest of the world combined).[46] This represents approximately 7% of their smoking population.

4. Cost of Service Comparison Issues

As with in-person interventions, quitlines cost more to deliver than wholly-automated services such as recorded messages and stand-alone websites due to personnel costs. However, the evidence base for recorded messages is nonexistent, and the evidence for stand-alone web interventions is nascent, with small effect sizes (see below). For many smokers, web-only interventions are unlikely to be acceptable as a complete substitute for human interaction.

Quitlines may be more expensive per quit than public policy changes that make continued smoking more onerous, such as increases in cigarette prices and clean indoor-air ordinances. Although primarily aimed at protecting nonsmokers, clean indoor-air ordinances and policies also denormalize smoking. Worksite smoking bans have been proposed as being more cost effective than cessation treatment as a means of getting individuals to quit.[47] However, public policy changes that make continued smoking more difficult can go only so far. In addition, policies that make it more challenging for people to smoke, without providing them with the tools to quit more effectively, inadvertently may discriminate against the most-vulnerable smokers, such as the highly addicted, poor, and those with psychiatric diagnoses, who find it harder to quit and have less access to help. Ideally, this is not an either/or question. When New York City went smoke-free in 2002, it simultaneously made nicotine patches and telephone counseling available, and saw the biggest decline in prevalence ever over a 1-year period recorded.[48]

It may be more appropriate to compare quitline costs, especially when delivered by health plans or employers or when funded through tobacco taxes or settlement dollars, to other healthcare service costs that add life-years to smokers. When compared to interventions such as lung transplants, lung-computed tomography screening, and coronary artery bypass, quitline costs are a clear bargain. For example, single-lung transplants, which may be performed in endstage chronic obstructive pulmonary disease (COPD) patients, result in an average increase in quality-adjusted life-years (QALY) of 2.1.[49] Transplants can cost hundreds of thousands of dollars per surgery, and the cost per QALY is estimated at $48,241. In comparison, phone counseling and medication support for quitting smoking cost well under $500, and add 3 to 10 years to life expectancy.[20,50]

5. Limitations of Quitlines

There are limitations to what can be accomplished via remote interactions. Some deeper nonverbal interaction cues are lost, although some smokers may prefer the increased anonymity of the phone. Current regulatory requirements make it more difficult to generate a prescription or to bill for services via the phone. For example, Medicare recently provided some coverage for tobacco treatment, but specifically excluded direct phone-only service.[51] This decision was not based on concerns about effectiveness, but rather on general Medicare policies that do not allow reimbursement for any services delivered over the phone other than minimal follow-up for covered face-to-face encounters with a physician or psychologist.

A related concern sometimes expressed about quitlines is that they may diminish utilization of community-based in-person services. There is no published evidence to support or refute this concern, and even if true, no evidence to support this being a public health issue in terms of net benefit to the individual or society. Most quitlines maintain databanks of available community resources, and part of the intervention process includes exploring interest in nonphone services. These databanks usually include health department–supported programs, voluntary programs (such as groups run by the cancer, heart, and lung associations), health plan and employer programs, and private programs. Some quitlines have formal triage processes where individuals are queried as to their interest in web, phone, and in-person support. Given the very low utilization and promotion of in-person cessation programs, it is possible the availability of a line with triage capability actually could increase uptake of these services. However, the California Smoker's Helpline looked at callers referred to community resources, and found only 6% actually followed-up with referrals.[52] Finally, there is some evidence that the availability of telephone support for those interested in quitting actually may increase healthcare provider delivery of brief interventions to smokers in busy clinics, as recommended by tobacco guidelines.

Top Ten Development and Research Opportunities for Quitlines

Promising innovations could increase the reach, effectiveness, and efficiency of quitlines even further. However, these need additional development and research. Ten of these are outlined below.

1. Use of a Chronic Care/Disease Management Approach with Quitlines

The USPHS Clinical Practice Guideline states that "tobacco dependence shows many features of a chronic disease."[3] In the past 5 years, considerable progress has been made organizing medical care for patients with chronic conditions in a more effective manner. This includes employing centralized disease management services that proactively use databases to identify people who are likely to benefit from services, and then enrolling the high-risk individuals in phone outreach programs via "opt-out" models that assume they will consent to receipt of services. A chronic care model that emphasizes restructuring the delivery model for primary care to focus on proactive management has also been developed and studied.[53]

To date most quitline activity has been delivered using an extended "episodic care" model. Individuals are recruited via mass media or other promotions. After enrolling, callers are supported for their initial quit attempt with "relapse-sensitive" call schedules heavily weighted toward the first month or two. The 70% to 90% of participants who relapse at any time in the process are considered treatment failures, but typically no modification in protocol or provision of additional services is provided. It is left up to the individual to call back at a future time to re-enroll, and in some instances there are limits on how soon this can be done. This model may not provide optimal service, given the chronic, relapsing nature of nicotine dependence and the very high stakes involved. In fact, it is now known that most smokers who have relapsed are interested in making another quit attempt almost immediately.[54] Given the considerable costs for promoting use of services, it may be ill-advised to continue to ignore smokers who have relapsed.

A number of alternative approaches with attributes of chronic care management are under development and investigation, including: (1) proactive outreach to high-risk populations such as asthmatics, diabetics, COPD patients, and pregnant women, where smoking status may be available; high acceptance rates (exceeding 50%) have been seen in population-based nonvolunteer recruitment studies of smokers offered proactive phone counseling[55]; (2) long-term follow-up and open-ended treatment, e.g., recurrent status checks with offers of re-enrollment for those who have relapsed; and (3) tighter integration with medical care, such as inserting chart notes into electronic health records with participating healthcare systems.

2. Integration of Phone Services with Other Remote Communication Media

Research in the area of integration and communication should focus primarily on: (1) web-based tailored content, social interaction via chat and discussion functions, and iterative quit plan interactive development tools; and (2) text messaging, cell phones, e-mail, and gaming.

The evidence base for these mediums is not as well established as the evidence base for phone counseling, but is growing. For example, a number of randomized trials have found modest but statistically significant improvements in quit rates for intervention participants who complete a fairly extensive survey, then receive deeply tailored cessation text and images at a website based on their answers.[56] Other forms of web support that focus on enhancing a participant's social support while providing a user-driven flexible menu of cessation information and exercises have less evidence. A large six-cell trial found a difference of a few percentage points, but only in a secondary analysis of the sites that were used more heavily.[57] Text messaging over cell phones was shown to be effective in creating a short-term (3-month) increased quit rate in a randomized

trial in New Zealand, including Maori users.[58] Although there is a strong established evidence base for phones that does not yet exist for these new media, they have potential advantages over standard phone-only quitlines, meriting further development and testing. For example, the new mediums: (1) may be cost effective in generating population-level quit attempts because they rely less on paid cessation counselors for delivery, even if the incremental quit rate improvement is modest; (2) are easily scalable; (3) are much more interactive and allow for more tailoring to the individual than printed materials; and (4) may appeal to people who enjoy new communications technology, or who find even phone counseling intimidating.

There have been no trials completed to date that examine more advanced, seamlessly integrated services that leverage the advantages of human interaction via phone, instant messaging, and e-mail with the efficiency of web-based and other e-communication encounters that do not require live input. However, several studies and development projects are underway, including randomized trials comparing modalities.

3. Further Integration and Innovation of Pharmacotherapy and Quitlines

The initial studies establishing quitline effectiveness predated pharmacotherapy, so there is a firmly established independent effect on long-term cessation achieved by phone coaching alone. Over the past 5 years, there has been increasing interest in using quitlines to address some of the challenges of how pharmacotherapy is used (or not used) in the real world.[59] These challenges include increasing proper use and adherence, ensuring quitters receive some instruction on the nonpharmacologic aspects of quitting, and increasing the fraction of quitters who use pharmacotherapy. Exactly how best to do this remains uncertain.

The following research areas are particularly in need of additional innovation and research: short-term nicotine replacement therapy (NRT), tighter relationships with healthcare providers to ease access to prescription-only medications for smoking cessation, and the safety, efficacy, and practicality of more aggressive pharmacotherapy approaches.

Offering brief courses of NRT through quitlines may be a more cost-effective way of generating calls than the use of mass media, and result in higher quit rates. New York City saw a marked increase in call volumes with a free patch offer in 2004, with almost 400,000 callers.[3] New York State examined the cost effectiveness of time-limited nicotine patch promotions versus traditional media promotion and found patch promotion to be highly cost effective.[60] Minnesota[61] and Oregon[62] also saw a marked increase in calls based solely on earned (nonpaid) media announcing patch availability.

There are less data on the relative cost effectiveness of short courses of NRT versus longer courses.

Research and innovation are also needed to forge tighter relationships with healthcare providers to increase ease of prescription medication access. Many quitlines have determined ways to connect medically appropriate callers directly with over-the-counter medications without requiring a physician visit, using careful protocol screening and mail order or pharmacy voucher fulfillment. A handful of integrated healthcare systems with phone counseling programs have created fulfillment protocols that include physician prescription authorization.

Finally, research should also encompass the testing of safety, efficacy, and practicality of aggressive cessation pharmacotherapy approaches, including: combination and higher-dose therapy, initiation of pharmacotherapy while still smoking, new medications and vaccines, "test kits," and aggressive medication management.

4. Impact of the "Ask-Advise-Refer" Model on Quitlines and Healthcare Practice

Many health plans and healthcare practices have struggled to implement the USPHS guideline 5A's model[63] (Ask, Advise, Assess, Assist, Arrange follow-up) of clinical practice that assumes all care for smokers is delivered by busy primary care teams. To increase adoption, quitlines have been proposed as part of an "Ask-Advise-Refer" model where the last three A's (Assessment, Assistance, and Arranging follow-up) can be handled predominantly by active referral to a quitline.[64] New quitline tools such as fax referral systems and feedback loops back to providers are being created and implemented to facilitate this model. There have been a number of trials that have examined the impact of this type of model, and it appears very promising.[21,65] However, there are unanswered questions, particularly regarding: (1) How many patients actually connect and receive service from quitlines, if they are referred by their healthcare provider? (2) Is a fax referral system more effective than a "call this number" approach? Which are healthcare providers more likely to adopt? (3) What is the clinic and population impact of "Ask-Advise-Refer" compared to the traditional clinic-based 5A's model?

5. Developing and Testing Improved and New Behavioral Interventions

The impact of varying the content of interventions delivered via quitlines has not been studied systematically. A recent British study by Gilbert et al.[66] did not find a quit rate difference between one and multiple calls, unlike most other previous studies. They posited that their failure may have been due to using a nonstructured, client-led protocol with counselors given

little guidance as to what to talk about, treating each call like a separate, unrelated encounter.

There are multiple ways the content of interventions could be varied to attempt to improve quit rates and satisfaction. Many of these approaches are not specific to phone counseling, i.e., it is not known if they improve outcomes in an in-person setting either. Examples include:

1. Decreasing nicotine content over time via fading, scheduled smoking, or denicotinized cigarettes. More sophisticated approaches that include hand-held devices to record use patterns and give realtime suggestions for scheduled smoking hold promise, and could be combined with quit coach availability.

2. Taking different theoretic approaches to coaching/counseling content. Trials specifically comparing the relative merits of Cognitive–Behavioral therapy, Motivational Interviewing, the 3 "T"s (creating motivational Tension, Triggering action, and Treatment availability)[67] or other theory-based counseling content, and determining their incremental added benefit compared to practical advice and social support will be helpful.

3. Examining the impact of increasing the number of calls or call time length on quit outcomes. A recent Veteran's Administration trial that obtained higher than usual quit rates offered more calls.[65] There is evidence from in-person programs that more contact can increase quit rates markedly.[68] One randomized trial found that 10–12 calls focused around the quit date increased 90-day abstinence rates at 6 months.[69] However, because of the increased cost implications, replication and further study of what subpopulations may benefit from increased intensity are needed.

4. Relapse-sensitive versus recycle-sensitive timing of calls. The trend in timing of phone counseling calls has been to frontload them around the caller's quit date (relapse-sensitive). This makes sense from the perspective of helping to prevent relapse. However, checking in with people over a more extended period also may be helpful to encourage those callers who have relapsed to call again (recycle-sensitive). Some earlier phone models stressed this approach.[70] There has never been a direct comparison of these two methods, nor of an integrated approach that does both.

5. More formative analysis of the experience of those going through treatment to identify modifiable influencers of success and relapse. This knowledge will benefit from the creation of multistate databases, and from more standardized processes and outcomes reporting so quit rates and influencers such as contact time can be compared reliably across states and service providers.

6. Cost Effectiveness of Different Promotional and Service Approaches

A quitline's population impact depends not just on quit rates, but even more so on how effectively it is promoted. Promotion is critical for two reasons; promoting the availability of a quitline may increase quit attempts in the general population, and it will determine how many people call to use the service. Much remains to be learned in this critical arena.

Quitlines vary significantly from each other and over time as to how much emphasis they put on different promotional strategies such as mass media, community awareness, and healthcare system and provider referrals. Measuring the impact of these approaches on quitline utilization is straightforward, but measuring the impact of different strategies on the rate of quit attempts in the general population that do not result in a call to the quitline is more challenging.

Development and research is needed to explore highly efficient methods for recruiting callers, such as the placement of the 1–800–QUITNOW number on cigarette packages. Incentive programs such as "Quit & Win" contests, which have been used internationally, as well as decreased health insurance premiums also show considerable promise.

A deeper understanding of what drives tobacco users to make quit attempts and what types of support services they would find most attractive could help in the re-engineering of both cessation services and promotion. The Robert Wood Johnson Foundation (RWJF) is sponsoring an initiative applying innovative product development approaches to increase consumer demand for cessation, including quitlines.

Further cost effectiveness and return-on-investment studies for likely high-yield populations such as COPD, obstetrics, diabetes, and asthma are needed. Most cost-effectiveness analyses have concentrated on the entire population of smokers. Analyzing high-utilization subpopulations may help make a stronger case to employers or health plans for aggressive intervention support.

7. Development and Testing of Proxy (Helper) Interventions

Quitlines primarily serve smokers interested in quitting, relying on media, public policies that denormalize smoking, and healthcare providers to increase motivation to quit and seek help. However, many family members, friends, coworkers, and other former smokers are interested in and can be taught basic cessation-support skills similar to those used by healthcare providers.[71] With no effort to recruit them, approximately 5% of calls to quitlines are from these proxy helpers. In some populations such as Asian immigrants, over 50% of calls are from proxies.[72] Can quitlines be used more vigorously and effectively as a source of information,

support, and skillbuilding for proxies? If so, will this help to motivate and then support smokers attempting to quit, including increasing use of evidence-based services?

8. Experiments in Coordination of Public–Private Benefits to Increase Reach of Quitlines

As noted earlier, lack of sufficient funding is a prodigious obstacle to further dissemination of quitline services. Improved surveillance and tracking of the impact of different approaches to funding, promoting, and delivering service on quitline utilization and outcomes, as well as conscious experimentation with different public–private mixes, may shed light on what approaches hold the most promise for long-term solutions. Examples include: (1) risk-based sharing of financing for service and promotion among different institutions, such as in Massachusetts where the state pays for counseling and health insurers pay for medications, or Minnesota where the settlement trust funds are used to pay for statewide promotion and triage, with full service reserved for the uninsured, while insurers pay for all phone counseling and medications for their members; and (2) more aggressive government-funded service such as in Australia and Maine, where over 8% of smokers receive quitline service. Can it be determined more quantitatively how heavy government provision of service affects healthplan/employer financing and delivery?

9. Tailoring of Service and Promotion for Subpopulations

There is considerable public health interest in creating different versions of quitline services and promotion for various groups that may be less prone to use or benefit from standard cessation support. Examples include Native American/Alaska Natives, Medicaid recipients, gays and lesbians, youth, seniors, blue-collar workers, smokers with mental health or substance abuse diagnoses, obese and overweight smokers, pregnant women, and other ethnic/racial groups. However, other than providing services in people's native languages and being sensitive to cultural differences, so far there is little or no evidence that taking a substantially different clinical approach makes a difference.[3] Is further population tailoring critical, given these groups' disproportionate prevalence or risk, or is it a distraction? Further surveillance, inquiry, and experimentation can help sort out whether focusing on better quitline publicity, cultural sensitivity, and accessibility will sufficiently serve the needs of these populations, or whether greater modification is necessary.

There is also a need to determine if tailoring treatment content, duration, frequency, and timing based on other individual characteristics (such as level of addiction, past quit history, and motivational attributes) improves outcomes.

10. Disseminating Quitlines in the Developing World

There are now over 80 quitlines in North America, Europe, and Australia/New Zealand.[73] There are only four in the developing world.[74] As developing countries that are signatories to the Framework Convention on Tobacco Control (FCTC) move to implement the cessation provisions, quitlines increasingly are being considered as a strategy. Quitlines can create an impact even where healthcare services are disorganized. In addition, promotional campaigns for quitlines help to normalize quitting, thus increasing the rate of quit attempts. Developing countries may be able to take advantage of low labor and media costs. However, they may also be hampered by less-developed telephone systems and more limited overall resources for delivery and evaluation.

For quitlines to be disseminated effectively to less well-developed countries, financial and systems support for knowledge and technical expertise transfer need to be developed. In addition, further development and research is needed to create and test less-expensive options for high-volume situations, such as recorded messages and very short courses of counseling and medication.

Research Implications

Quitlines are creating a remarkable infrastructure for theoretic and applied research in numerous disciplines. They are collecting uniform minimum datasets on hundreds of thousands of tobacco users who attempt to quit each year. In the U.S., there is wide heterogeneity in recruitment and service strategies from state to state and institution to institution, providing numerous natural experiments. Because of the high volume of participants and computerized coaching support, quitlines also provide opportunities for "easy" large-scale social science, health services research, pharmacologic effectiveness, and other randomized trials to test theoretic models as well as to conduct practical clinical trials relating to cost effectiveness and equivalency of different approaches.

This new infrastructure for research is only beginning to be utilized to the extent possible. Despite having developed and implemented a state-level minimum data set, this data has not been integrated and analyzed even for basic information about the demographics of quitline users. New models to encourage and support quitline research are needed that take advantage of their ability to answer scientific and practical questions quickly and efficiently.

Conclusion

The new behavioral technology that formed the basis of quitlines easily could have languished in articles growing moldy on the shelves of libraries; instead, individuals in academia, state health departments, healthcare companies, philanthropic organizations, federal agencies, large employers, and service agencies created a vision and over time brought it to life. This has been a messy, sometimes painful process that never would have gotten as big as it has if the individuals involved had not seen its potential to improve individual and public health, and if they had not worked and argued together to make it real. The glass is now hopefully only half full, and much more will be discovered and done to further maximize the potential of this potent tool to help disseminate evidence-based treatments.

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Changing Smokeless Tobacco Products
New Tobacco-Delivery Systems

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Abstract: Smokeless or noncombusted oral tobacco use as a substitute for cigarette smoking has been gaining greater interest and attention by the public health community and the tobacco industry. In order for the product to appeal to smokers, tobacco companies have been manufacturing new noncombusted oral tobacco (i.e., moist snuff) that is lower in moisture content and nitrosamine levels, packaged in small sachets and "spitless." While the primary motives of the major tobacco companies are to maintain or increase tobacco use, some members of the public health community perceive the use of noncombusted oral tobacco products as a harm reduction tool. Because cigarette smoking is associated with greater toxicant exposure compared to noncombusted oral tobacco, reduced mortality and morbidity are hypothesized to ensue, if cigarette smokers switched completely to these products. However, variability exists in levels of nicotine and toxicants and potential health consequences from use within and across countries. Therefore, promulgating noncombusted oral tobacco products as a safer alternative to smoking or as a substitute for smoking may engender more rather than less harm. To date, limited research is available on the effects of marketing noncombusted oral tobacco products to smokers, to support the use of these products as a harm reduction tool, and to determine the effects of varying levels of tobacco toxicants including nicotine on health. The need exists for manufacturing standards to lower toxicant levels of all noncombusted oral tobacco products, for the formulation of appropriate tobacco-product regulations and for the development of a strategic plan by the public health community to address this controversial topic.
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Introduction

Marketing strategies and types of available smokeless tobacco products have been evolving in the United States. Products are being manufactured to appeal to cigarette smokers (e.g., spitless, in small tea-like packets, different flavorings) and promoted to be used in situations where they cannot smoke or as a substitute or alternative to smoking. The U.S. Smokeless Tobacco Company (USSTC; Greenwich CT) filed a request for an Advisory Opinion with the Federal Trade Commission (FTC) seeking guidance "regarding the acceptability of communicating in advertising that smokeless tobacco products are considered to be a significantly reduced risk alternative as compared to cigarette smoking" (letter submitted in February 2002, withdrawn August 2002, additional information submitted in May 2003). The availability and

marketing of these products address two primary concerns faced by cigarette smokers: increasing bans on smoking and health risks associated with smoking. For tobacco companies, these products may serve to maintain tobacco use among existing smokers and to recruit new tobacco users.

In the public health community, smokeless tobacco use as a complete substitute for cigarette smoking or as a method of cessation is gaining support, but remains hotly debated. Tobacco harm-reduction approaches, such as the use of smokeless tobacco among smokers unwilling or unable to quit, have been considered as a feasible alternative that can potentially reduce tobacco-related morbidity and mortality, even with continued use of products that contain tobacco constituents.[1] A thoughtful, unbiased examination of the feasibility of methods to reduce tobacco-related harms that do not preempt other tobacco-control measures such as prevention and cessation is urgently needed. Currently, cigarette smoking is the leading cause of death in the U.S., accounting for approximately one in six deaths (438,000 each year) and 5.5 million years of potential life lost. In 2005, approximately one fifth (45.1 million) of the U.S. adult population were smokers.[2] Although an estimated 70% of smokers (33.2 million) would like

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to quit, successful long-term abstinence remains low (2.5% or 1.2 million smokers per year).[3,4] Worldwide, approximately 1.3 billion people smoke and about 4.9 million die from tobacco-related illnesses each year. If present consumption patterns continue, an estimated 10 million people will die each year from tobacco-related disease by the year 2020.[5,6]

Excepting nicotine pharmaceuticals, of the various currently available potential reduced exposure products (PREPs) that may result in actual harm reduction, smokeless tobacco products have the greatest potential to reduce risk for disease if smokers completely switch from cigarettes to these products. For example, the relative risk for disease with "low-nitrosamine" smokeless tobacco is considered to be at least 90% less than cigarette smoking.[7] In a report by the Tobacco Advisory Group of the Royal College of Physicians,[8] smokeless tobacco use is considered 10–1000 times less hazardous than cigarette smoking, depending on the product. Unlike cigarette smoking, smokeless tobacco use has not been linked to many of the smoking-related cancers[9,10] or to pulmonary disease.[11] Epidemiologic data from Sweden have been used to support the hypothesis that switching from cigarettes to smokeless tobacco products can significantly reduce tobacco-related morbidity and mortality among tobacco consumers. A reduction in lung cancer in Sweden has been observed in men. This reduction has been attributed by some investigators to the increased use of "snus" (i.e., Swedish snuff) and a corresponding reduction in cigarette smoking.[12,13] The decline in smoking has not been as dramatic in women, potentially due to the limited uptake of snus among women. Other researchers have debated this interpretation based on the observation that the prevalence of smokeless tobacco use is "not consistently associated with a reduction in smoking initiation or prevalence."[14] Many public health scientists and advocates are concerned that the Swedish experience would not be replicated elsewhere. However, if a significant number of current smokers who would not have otherwise quit switched completely to "low-nitrosamine" oral tobacco products, then a significant reduction in prevalence of tobacco-related disease is likely to occur.[7]

The aims of this article are to describe the extant literature on newer smokeless tobacco products directed at smokers, the currently existing literature on the toxicity of these products, including nicotine addiction, and future directions for research.

Types of Smokeless Tobacco Products

Several types of smokeless tobacco products are available which can be administered orally or nasally. Moist snuff is finely ground or shredded tobacco sold either loose or in packets (i.e., sachets) and used orally. A user places a pinch or dip between the cheek and gum. Dry snuff is fine powdered tobacco and can be used either orally or nasally. Chewing tobacco comes as twist, plug, or loose leaf. The user places a "wad" of this product inside the cheek. Moist snuff and chewing tobacco may require spitting and therefore has been referred to as "spit tobacco." Other smokeless tobacco products are tobacco mixed with other substances. Alaskan natives, for example, mix tobacco leaves with ash from a woody fungus that grows on the bark of birch trees (i.e., punk ash). This product is frequently referred to as Iq-mik.[15] In India, Southeast Asia, or the United Kingdom, tobacco is mixed with areca nut, lime, flavorings, or spices and is either manufactured or handmade (e.g., betel quid in India). Newer products being marketed primarily to cigarette smokers are sold as pouched, "spitless" moist snuff or compressed tobacco lozenges. Swedish Match (Stockholm, Sweden) introduced a Swedish snus, Exalt, to the U.S., but this product is no longer sold in this country. The processing of Swedish snus involves heat treatment or pasteurization rather than fermentation. This leads to lower levels of tobacco-specific nitrosamines (TSNAs) than in some American products. Furthermore, Swedish Match has introduced voluntary standards, called GothiaTek® (www.gothiatek.com) that set limits for oral tobacco constituents, and specify standards for manufacturing and for the provision of consumer information. Because snus is included in the Swedish Food Act, only additives and flavorants that are permitted in foods are allowed in snus. In addition, Swedish Match reports that the nontobacco-specific compounds have established limits that are comparable to food products. The manufacturers recommend that retailers refrigerate the products to keep them "fresh" (e.g., prevent further nitrosamine formation) and to meet the "best-before" criteria.

The U.S. Smokeless Tobacco Company (USSTC) introduced Revel in 2001. This product is marketed as a "unique, discreet option for adult smokers seeking an alternative that allows them to enjoy real tobacco satisfaction without lighting up." Revel was developed "for smokers living in a no-smoking world" and is described as "not like nicotine gum or tobacco-cessation product." The products are 100% American tobacco and available in mint, wintergreen, and cinnamon. In 2006, USSTC manufactured and now is test-marketing Skoal Dry, which is likely to replace Revel. This product uses a bigger pouch than Revel and comes in regular and mint flavors. The method of curing and processing of these products is publicly unknown. Also, in 2006, Camel Snus (marketed by Reynolds American, Inc., Winston-Salem NC) and Taboka Tobaccopak (manufactured by Phillip Morris, Richmond VA) were introduced for test marketing. Camel Snus is manufactured by Swedish Match and adheres to the same manufacturing standards as the other Swedish snus products. Furthermore, retailers store Camel snus in a chilled container, but the product does not have to be
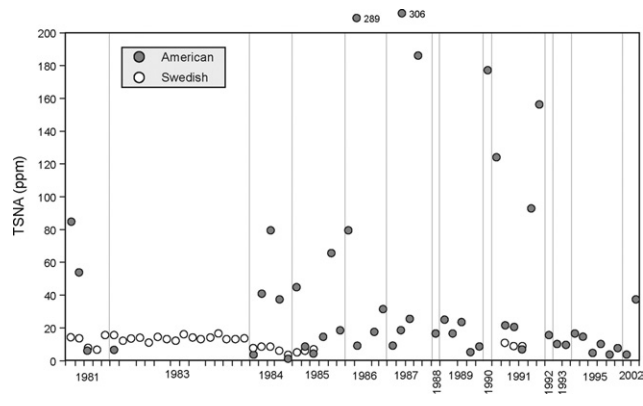
Figure 1. Historic levels of tobacco-specific nitrosamines in noncombusted oral tobacco products.[25]
ppm, parts per million; TSNA, tobacco-specific nitrosamine.

refrigerated during use. Camel snus is sold in spice, menthol, and original flavors. Taboka, similar to Swedish snus, contains pasteurized tobacco. However, compared to Swedish snus, this product is lower in moisture content, includes a flavor-strip technology, has a reduced salt content, and does not require refrigeration. It comes in original (Taboka) or mint (Taboka Green) flavors. Recently, Phillip Morris announced that it was test-marketing Marlboro snus.[16]

In 2001 and 2003, Star Scientific (Chester VA) introduced two smokeless tobacco potentially-reduced-exposure products, Ariva and Stonewall. Ariva was also designed to be used by smokers in situations where they cannot smoke, while Stonewall was designed as an alternative to moist snuff.[17] Both products have been through the process of "Star-curing," an innovative method of curing tobacco which may nearly eliminate the TSNAs, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N′-nitrosonornicotine (NNN), from the tobacco. Star-curing is a patented two-step process that does not involve chemicals, solvents, or other additives. The leaf is dried in a barn for approximately 24–36 hours at about 100–110°F, until it turns yellow. It is then pressed to remove moisture and microwaved until moisture is reduced by an additional 10%.[18] According to research by Star Scientific and independent sources, the StarCured process preserves the normal nicotine and monoamine oxidase (MAO) inhibitor content, while reducing TSNAs to "almost undetectable levels."[19,20]

The newer smokeless tobacco products make the term "spit tobacco" seem antiquated. Furthermore, because newer cigarette-like devices that are being developed have been shown to emit minimal second-hand smoke,[21] the term smokeless tobacco appears to lack specificity. In this paper, these products are predominantly referred to as "noncombusted oral tobacco products," which seems to be a more specific and descriptive terminology for the current "smokeless tobacco" products.

Toxicants of Noncombusted Oral Tobacco Products

Although oral tobacco products lack the toxicants associated with combustion, they include 28 known carcinogens.[22] Some of these carcinogens are TSNAs. The TSNAs that have been most strongly linked to cancer are NNK and NNN. These TSNAs are formed during curing, processing, and aging of tobacco and are present in both burned and unburned tobacco. According to the International Agency for Research on Cancer (IARC), these TSNAs are considered Group 1 carcinogens. They cause tumors of the oral cavity, esophagus, pancreas, and lung in laboratory animals.[23,24] The TSNAs in some noncombusted oral tobacco products manufactured in Sweden and the U.S. have decreased over time. Products in Sweden are now typically below 10 ppm and products in the U.S. are typically below 20 ppm (Figure 1).[25] Several studies have examined amounts of TSNAs in oral tobacco products in various countries.[26–30] Figure 2 shows a compilation of a few of the recent studies that have measured NNN and NNK in the U.S.,[28] Sweden,[30] and India[29] and illustrates three primary points. First, there is a wide variability in carcinogen levels among oral tobacco forms found in the U.S., Sweden, and India. The highest levels reported are found in a product made in Sudan called toombak, which is a mixture of tobacco and sodium bicarbonate (amounts not shown in Figure 2). The levels of TSNAs in this type of product are in the thousands of micrograms per gram dry weight.[26] Second, there are significant differences in TSNAs among the various U.S. brands despite the general decrease in overall levels of carcinogens (Figure 1). These differences occur even within the same U.S. brand bought in different locations[31,32] (e.g., Copenhagen had NNK values varying from 1.45 to 3.20
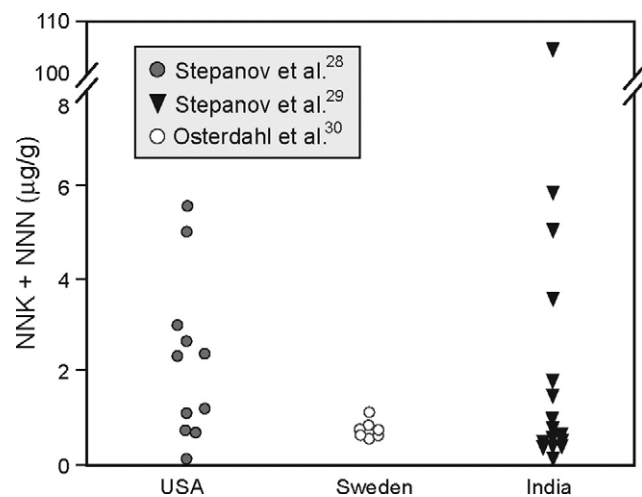

Figure 2. NNK and NNN levels in noncombusted oral tobacco products across and within countries.
NNK, 4‑(methylnitrosamino)‑1‑(3‑pyridyl)‑1‑butanone; NNN, nitrosonornicotine.

Table 1. Tobacco-specific nitrosamine levels[28]

Tobacco products	Tobacco-specific nitrosamine level (μg/g product wet weight)				
	NNN	NNK	NAT	NAB	Total
New tobacco products					
Hard snuff					
Ariva	0.019	0.037	0.12	0.008	0.19[a]
Stonewall	0.056	0.043	0.17	0.007	0.28[b]
Swedish snus					
General	0.98	0.18	0.79	0.06	2.0[c]
Spit-free tobacco packets					
Exalt					
Purchased in Sweden	2.3	0.27	0.98	0.13	3.7[d]
Purchased in the U.S.	2.1	0.24	0.68	0.05	3.1[b]
Revel					
Mint flavor	0.62	0.033	0.32	0.018	0.99[b]
Wintergreen flavor	0.64	0.032	0.31	0.017	1.0[b]
Camel Snus					
Original	0.79	0.16	0.19	0.008	1.15[b]
Spice	0.87	0.09	0.20	0.010	1.17[b]
Frost	0.83	0.16	0.13	0.006	1.12[b]
Taboka					
Taboka	0.91	0.06	0.30	nd	1.27[b]
Taboka Green	0.82	0.07	0.24	0.002	1.13[b]
Nicotine replacement therapy products					
NicoDerm CQ (patch, 24-mg nicotine)[e]	nd	0.008	nd	nd	0.008[b]
Nicorette (gum, 4-mg nicotine)[e]	0.002	nd	nd	nd	0.002[b]
Commit (lozenge, 2-mg nicotine)[e]	nd	nd	nd	nd	nd[b]
Conventional smokeless tobacco products					
Copenhagen					
Snuff	2.2	0.75	1.8	0.12	4.8[b]
Long cut	3.9	1.6	1.9	0.13	7.5[b]
Skoal					
Long cut straight	4.5	0.47	4.1	0.22	9.2[b]
Bandits	0.9	0.17	0.24	0.014	1.3[b]
Kodiak					
Ice	2.0	0.29	0.72	0.063	3.1[b]
Wintergreen	2.2	0.41	1.8	0.15	4.5[b]

[a]Mean of five analyses, each performed in duplicate.
[b]Single analysis performed in duplicate.
[c]Mean of two analyses, each performed in duplicate.
[d]Mean of three analyses, each performed in duplicate.
[e]Values are expressed per piece.
NNN, N'-nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NAT, N-nitrosoanatabine; NAB, N-nitrosoanabasine; nd, not detected.

μg/g dry weight with a coefficient of variation of 32.9%[32]) and can vary depending on length of time on the shelves.[33] Products manufactured in Sweden and sold in the U.S. also show some variability and higher levels of TSNAs than the snus products sold in Sweden.[28] The differences in TSNAs among oral tobacco products used in India are more dramatic with values ranging from 1.2 to 128 μg/g product wet weight. Third, products in Sweden tend to have uniformly lower nitrosamine levels than American products, which is, in part, due to the GothiaTek® standards developed and adhered to by the manufacturers of Swedish snus.

Table 1 shows data on the newer oral tobacco products[28] introduced in the U.S. This table clearly demonstrates that the levels of total TSNAs are highest in the conventional and most popular oral tobacco products

sold in the U.S (i.e., Copenhagen and Skoal),[34] with TSNAs ranging from 4.8 to 9.2 μg/g product wet weight. The Swedish products such as General Snus and Exalt are somewhat lower in TSNAs with values ranging from 2.0 to 3.7 μg/g product wet weight. The lowest levels of TSNAs are observed in oral tobacco products manufactured by Star Scientific, tobacco lozenges such as Ariva and Stonewall, 0.19 and 0.26 μg/g product wet weight, respectively. The medicinal nicotine products tended to have extremely low or nondetectable levels of nitrosamines.

A critical question is how the levels of nitrosamines in tobacco products translate into the uptake of carcinogens in humans. Figure 3 shows the results from a compilation of studies that had been conducted. The concentrations of metabolites of NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-butanol [NNAL]
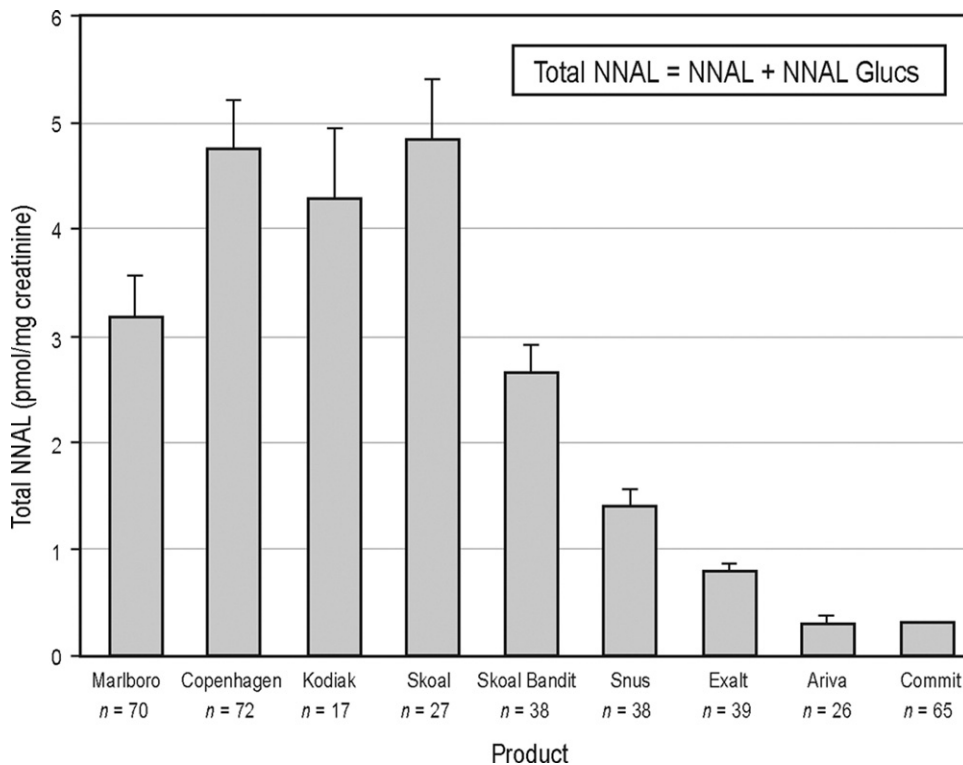
Figure 3. Total NNAL concentrations in urine: users of different brands of noncombusted oral tobacco products, medicinal nicotine (Commit), and Marlboro cigarettes.
NNAL, 4-(methylnitrosamino)-1-(3-pyridyl)-butanol.

and its glucuronides [NNAL-Glucs] or total NNAL, which serves as a biomarker for exposure to carcinogens, were examined across different brands of noncombusted oral tobacco products and compared to Commit (GlaxoSmithKline, Pittsburgh PA), a medicinal nicotine that is FDA-approved for smoking cessation. These data represent analyses of the information collected from separate studies[35–39] and some of the studies involved subjects who were noncombusted oral tobacco users while others involved cigarette smokers who switched to noncombusted oral tobacco products. In spite of these limitations, the concentrations of total NNAL parallel the NNK levels in these products. This figure also illustrates the diversity of toxicant uptake across products and that some of the more conventional oral tobacco products result in higher total NNAL levels than smokers of Marlboro cigarettes, providing a cautionary note that switching to noncombusted oral tobacco products does not necessary result in reduced toxicant exposure.

Unfortunately, the majority of existing studies have examined the human uptake of only a few of the carcinogens in these products.[36,37,39–44] Table 2 lists other carcinogens that have been found in noncombusted oral tobacco products. To obtain an accurate picture of the potential harm associated with these products, a more comprehensive assessment of the levels and uptake of toxicants in these products is

necessary. Additionally, it is notable that these data are over 20 years old and require updating.

Reduction of Toxicant Exposure in Noncombusted Oral Tobacco Users and Cigarette Smokers

The variability of toxicants in noncombusted oral tobacco products begs the question of whether users of high nitrosamine cigarettes or "traditional" smokeless tobacco products can reduce their level of toxicant uptake through product substitution. Unfortunately, few studies have addressed this question. The studies conducted to determine the effects of switching smoke-

Table 2. Other carcinogens in processed tobacco[45,46]

Carcinogen	Amount (per gram)
Benzo[*a*]pyrene	0.1–90 ng
Formaldehyde	1.6–7.4 μg
Acetaldehyde	1.4–7.4 μg
Crotonaldehyde	0.2–2.4 μg
1,1-Dimethylhydrazine	60–147 ng
Ethyl carbamate	310–375 ng
Hydrazine	14–51 ng
Arsenic	500–900 ng
Nickel	2–6 μg
Chromium	1–2 μg
Cadmium	1.3–1.6 μg
Lead	8–10 μg
Polonium-210	0.2–1.2 pCi

less tobacco users to a lower nitrosamine noncombusted oral tobacco product demonstrate that a significant reduction in toxicants can occur.[35,36,39] In one study, Copenhagen and Kodiak users were randomly assigned to General Snus, a Swedish product with about 60 to 75% lower NNK than the leading U.S. smokeless tobacco brands, or to nicotine patch for a period of 4 weeks. The results showed a significant reduction in concentrations of total NNAL when subjects switched from their usual brand to General Snus (about 50% reduction compared to baseline), but a significantly greater reduction with the nicotine patch (about 90% reduction compared to baseline[35]). In another study, Copehagen or Skoal Original users were switched to Skoal Bandits, which is lower in TSNAs.[36] Again, a significant reduction in total NNAL was observed, with concentrations that were similar to those observed with General Snus. General Snus is higher in nicotine content than Skoal Bandits and surprisingly, very little increased use of Skoal Bandits was observed even with this low nicotine content. Both these studies would indicate that smokeless tobacco users can significantly reduce their toxicant exposures by switching to a product with lower TSNAs.

Similarly, few studies have addressed whether or not cigarette smokers can reduce their toxicant exposure if they switched to the noncombusted oral tobacco products. Two pilot studies were conducted using a within-subject crossover design in which subjects were assigned, in randomized order, to medicinal nicotine lozenge for 2 weeks and an oral tobacco product for 2 weeks.[39] The oral tobacco product in the first study was Exalt, a Swedish Match snus product in a sachet. In the second study, the oral product was Ariva, a tobacco lozenge. The results from the first study showed that both Exalt and the nicotine lozenge resulted in a significant reduction in total NNAL concentrations; however, the nicotine lozenge led to a significantly greater reduction in total NNAL concentrations. In the second study, significant reductions in total NNAL concentrations were observed for both the nicotine lozenge and Ariva and the levels of reduction were similar. The main point of these studies is that smokers can dramatically reduce their exposure to a tobacco-specific carcinogen when they switch to lower nitrosamine oral tobacco products. Whether or not this reduction would reduce the risk for adverse health outcomes is unknown.

Health Effects from Noncombusted Oral Tobacco Products

In the U.S. in 2005, 7.7 million (3.2%) of Americans aged 12 or older were current (past month) noncombusted oral tobacco users.[47] Noncombusted oral tobacco use in the U.S. is higher among whites, men, American Indians/Alaska natives, people living in southern or north central states, and among people who are employed in blue-collar occupations, service/laborer jobs, or are unemployed.[48] In India, it is estimated that 22% of men use noncombusted oral tobacco exclusively, and 8% use noncombusted oral tobacco and smoke concomitantly.[49] Approximately 23% of Swedish men report use of noncombusted oral tobacco (i.e., snus).[13] In Sudan, about 40% of men and 10% of women use noncombusted oral tobacco (i.e., toombak).[50]

Although the overall exposure to toxicants with noncombusted oral tobacco is significantly lower than with cigarettes, oral tobacco is addictive and not safe. The controversy centers on whether these products should be promoted as safer than cigarettes with the risk of the unintended consequence of misleading consumers into assuming they are safe.

As summarized by Critchley et al.,[51] extant literature on the adverse effects of noncombusted oral tobacco is comprised of many studies with insufficient power to estimate precise risks, methodologic limitations, and inconsistency of findings, as well as by a paucity of studies on noncancer health effects. However, these studies provide the only means of assessing potential risks associated with use of these products. No data are available on the health effects of the newer "low-nitrosamine" noncombusted oral tobacco products aimed toward cigarette smokers. But, parallel to observations made with toxicant-concentration levels, the available literature suggests that adverse health consequences may vary by product type which is strongly associated with geography and the country of product origin.[13,51] For example, some of the noncombusted oral tobacco products used in India have high concentration of TSNAs compared to products from other countries (i.e., Sweden and U.S.), and India also has the highest estimated deaths from oral cancer.[27,51] In the U.S. where moist snuff widely used, the estimated number of deaths from oral cancer may be higher than in Sweden where snus is used.[51] To date, published studies predominantly relate to oral tobacco product use in the U.S., Sweden, and India.[13,51,52]

The link between oral tobacco use and adverse cardiovascular outcomes has been controversial.[51] A recent large, multinational case-control study observed an association between nonfatal acute myocardial infarction (AMI) and chewing tobacco use.[53] However, the small number of snuff users precluded the ability to draw conclusions about the effects of this form of tobacco on AMI risk. In the U.S., data from the Cancer Prevention Study-I (CPS-I) and CPS-II suggest that current chewing tobacco and snuff use is associated with an increased risk of death from coronary heart disease and cerebrovascular disease.[54] In Sweden, an early case–control study observed a higher risk of death from all cardiovascular conditions among snus users.[55] However, four Swedish population-based case–control

studies observed no association between moist snuff and the incidence of myocardial infarction[56–58] or stroke.[59]

The relationship between oral tobacco use and the development of risk factors for cardiovascular disease (i.e., metabolic syndrome and diabetes) is also conflicting. High consumption of Swedish snus has been associated with the development of metabolic syndrome (i.e., obesity, impaired glucose regulation, dyslipidemia, and hypertension).[60] An association between snus use and diabetes has been observed in one study[61] but not in another.[62] In the U.S., data from the CPS-I and CPS-II suggest no relationship between smokeless tobacco use and diabetes.[54]

Data from the U.S., Sweden, and India suggest an association between oral tobacco use and adverse health consequences for pregnant mothers and their fetuses. Oral tobacco (i.e., snuff) use in Sweden has been associated with lower birthweight, increased pre-term delivery, and increased rate of pre-eclampsia.[63] Among Alaska natives who use Iq'mik, oral tobacco use is associated with neurobehavioral changes in newborns.[64] In India, the use of oral tobacco is associated with an increased risk for preterm delivery, low birth-weight, and stillbirth.[65,66] Oral tobacco use in India has also been associated with a general decrease in reproductive health.[67]

Available data suggest a strong association between oral tobacco use and extra-oral cancer in India with several reports of an association from the U.S. and Sweden. In India, oral tobacco use has been associated with esophageal cancer.[68] In the U.S., data from CPS-I suggested an association between current smokeless tobacco use and death from cancer of the digestive system, and data from CPS-II observed a similar association for all cancer.[54] An association between oral tobacco use and kidney and pancreatic cancer was suggested by two U.S. case-control studies.[69,70] Two Swedish studies found no association between snus use

and gastric or esophageal cancer[71,72] but one observed an association with pancreatic cancer.[73]

A systematic review of the literature concluded that available data strongly and consistently support an association between oral cancer and oral tobacco use in India, which leads to approximately 10,000 deaths annually.[51] Data from the U.S. suggest an association between oral cancer and oral tobacco use.[74,75] However, the U.S. data have been limited by small sample sizes and inadequate power to detect significant risks. Swedish studies have not shown an increased risk for oropharyngeal cancers among current oral tobacco users.[76,77] Importantly, the IARC Monographs Working Group has reviewed the available evidence and has concluded that "there is sufficient evidence that smokeless tobacco causes oral cancer and pancreatic cancer in humans" and that smokeless tobacco is "carcinogenic to humans."[78]

No literature is available to elucidate if cigarette smokers or users of high-nitrosamine tobacco products who switch to low-nitrosamine products can reduce significantly their risk for disease.

Addiction Potential of Products

The addiction potential of a drug is also considered a tobacco-related harm. The addiction potential of a tobacco product depends on the amount of nicotine that is absorbed and the speed of nicotine delivery; the greater the magnitude of nicotine absorption and the faster the rate of absorption, the more addictive the product. The amount and speed of systemic absorption of nicotine are dependent on the product pH, nicotine content, and route of administration, with cigarette smoking resulting in the fastest rate of delivery. pH levels determine the amount of free nicotine. Higher pH levels (i.e., more alkalinity) create more free nicotine available for absorption in the bloodstream. Free or non-ionized nicotine is more readily absorbed

Table 3. Nicotine content in noncombusted oral tobacco products

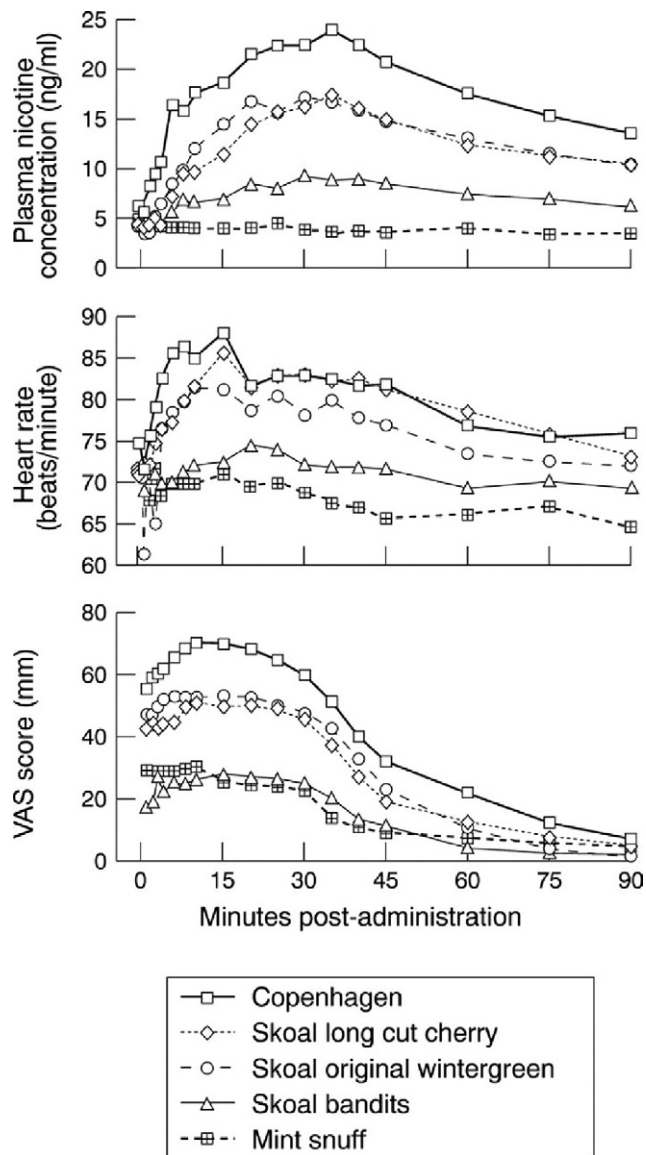| Dose	Product	pH	Nicotine content (mg/g)	Free nicotine (mg/g)
Low	**Hawken**[31,82,84]			
	Wintergreen	5.2–5.7	3.2–4.3	**0.01–0.02**
	Skoal Bandits[31,84]			
	Straight	5.2–5.4	7.9–10.1	**0.02–0.03**
	Skoal Bandits[31,82,83]			
	Wintergreen	6.9–7.1	7.1–8.5	**0.5–1.0**
Medium	**Skoal Long Cut**			
	Straight[82,83]	7.5–7.6	10.3–12.9	**2.4–3.7**
	Wintergreen[31,83]	7.4–7.8	10.5–11.0	**2.0–4.1**
	Cherry[83]	7.5	11.4	**2.6**
	Skoal Original[83]			
	Wintergreen	7.6	10.4	**2.9**
High	**Kodiak**[31,82,84]			
	Wintergreen	8.2–8.4	8.6–10.9	**5.8–6.5**
	Copenhagen[31,82–84]	7.6–8.6	11.1–12.7	**3.1–9.4**

Figure 4. Mean plasma nicotine concentration, heart rate, and visual analog scale (VAS) score (product "strength") after administration of each of four oral tobacco products or mint snuff.[85]

through cell membranes than ionized nicotine. Oral tobacco products vary widely in pH and nicotine levels.[26,31,33,79–82] Table 3 shows the amount of free nicotine in different oral tobacco products. The products with the highest free-nicotine levels are the most popular conventional brands (e.g., Copenhagen and Kodiak) used in the U.S., whereas products low in free-nicotine levels have lower use prevalence.[47] The free-nicotine content of the oral tobacco products parallels the plasma nicotine concentrations, as seen in Figure 4. Furthermore, the plasma-nicotine concentrations determine the perceived strength of the dip and the physiologic response.[85]

To date few studies have examined the free-nicotine content of the newer oral tobacco products. Table 4 presents the nicotine content in some of these products.[86] In a recent study that examines the pharmacokinetics of the newer oral tobacco products,[87] products such as Ariva and Revel result in very low nicotine concentrations, whereas product such as Stonewall had concentrations that were comparable to 4-mg medicinal nicotine lozenges. Copenhagen showed the most rapid absorption and highest concentration of nicotine. The peak nicotine concentration is similar to concentrations observed for cigarettes.[88] Products such as Taboka have relatively low nicotine concentrations (data presented by Phillip Morris at a meeting at the Harvard School of Public Health), whereas Camel Snus is reported to have nicotine amounts that are similar to Camel cigarettes and blood nicotine concentrations potentially similar to levels in cigarette smokers (www.snuscamel.com). This information has not been publicly released by the manufacturers and the products have not been made widely available for analysis.

The pattern of use for low- and high-nicotine products requires research. The low-nicotine products have the advantage of being lower in addictive potential, but may not be readily used by oral tobacco users or may not provide a good substitute for cigarette smoking, potentially leading to dual use of the cigarettes and noncombusted oral tobacco products. The high-nicotine, low-nitrosamine products have potential for abuse and to sustain addiction, but may provide a better substitute for more toxic tobacco products such as cigarettes.

Summary

In summary, noncombusted oral tobacco products are changing. These products are now being targeted to cigarette smokers for use in situations where a smoker cannot smoke or as an alternative to smoking. They are manufactured to appeal to smokers. Although these products contain lower levels of total carcinogens compared to cigarettes or the most popular conventional brands of oral tobacco products sold in the U.S. or in the world, some of these products still contain considerable amounts of carcinogenic nitrosamines which are far higher than those permitted in food.[89] To date, medicinal nicotine products have the lowest toxicant concentrations. The amounts of free nicotine in these noncombusted oral tobacco products vary widely as well. Some of these newer products contain significant amounts of nicotine, whereas other products contain

Table 4. Nicotine content of newer noncombusted oral tobacco products marketed as alternatives to cigarette smoking[82]

Product	pH	Nicotine (mg/g)
Stonewall	7.7	1.5
Revel	7.2	1.1
Ariva	7.4	0.6

low levels of nicotine. The consequent pattern and persistence of use may depend on the nicotine content of the product but there are no data to determine this relationship.

Future Directions and Research

One of the conclusions in the Institute of Medicine (IOM) report, Clearing the Smoke,[1] was the following: "Regulation of all tobacco products, including conventional ones as recommended by the IOM,[90] as well as all other PREPs is a necessary precondition for assuring a scientific basis for judging the effects of using PREPs and for assuring that the health of the public is protected." The necessity for regulation of tobacco products is supported by: (1) the data showing tremendous variability in levels of toxicants in these products, (2) the capability of producers to reduce toxicant levels in tobacco products and to control degree of potential product addiction, and (3) the need for independent scientific evaluation of these products. Renewed efforts to discuss and implement the regulation of tobacco products is critical to: (1) significantly improve the public health of this nation, (2) ensure that any deceptive practices of the tobacco industry are caught, (3) not have to rely on litigation as the only method to set limits on these deceptive practices, and (4) ensure that consumers are provided accurate information. The research that is necessary to understand the public health impact of these products is extensive[91,92] and includes preclinical and clinical research, consumer testing, and post-marketing surveillance.

Preclinical Research

Examine and identify the toxic constituents of the products and determine factors that may alter the levels of these toxicants including nicotine (e.g., shelf time, heat); and undertake in vitro and in vivo studies determining the toxicity of these products on cells and animals.

Clinical Research

Conduct human clinical trials that: (1) determine factors associated with palatability and maintenance of use of these products; (2) examine the uptake of toxicants using biomarkers for exposure and toxicity associated with different disease states[93]; (3) examine the natural pattern of use of these products as a cessation tool, as a substitute for smoking in situations where smoking is prohibited or people cannot smoke, or as a method to reduce smoking and determine the toxicant exposure associated with these patterns of use; and (4) conduct clinical trials with noncombusted oral tobacco products as a cessation tool compared to existing pharmacologic therapies in an effort to improve existing cessation medications if noncombusted

oral tobacco products prove to be more efficacious. For example, development and approval of medications that have more rapid absorption of nicotine, higher levels of nicotine and greater palatability may be critical to compete against more toxic noncombusted oral tobacco products.

Consumer Testing

Conduct consumer testing of these products to: (1) examine how the labeling, messages, promotion, marketing and placement of these products affect consumer perception of these products; (2) determine how consumer feelings, beliefs, attitudes, and knowledge affects uptake or manner of use of these products; and (3) determine methods for labeling, messaging, promotion, marketing and placement of products that would reduce public health harm associated with the use of these products.

Post-Marketing Surveillance

Conduct post-marketing surveillance of these products to determine: (1) who is using them; (2) how they are being used; (3) toxicant exposure; (4) potential health harms associated with their use; (5) whether they serve as a gateway or substitute for cigarette smoking; and (6) the extent to which their introduction and marketing increases uptake, maintenance or relapse to tobacco products.

As a final word, the potential to do harm or to benefit the public health by the introduction of these products is tremendous. To circumvent public health harm, an infrastructure and funding that allow comprehensive and collaborative research efforts are necessary. To date, examination of the toxicity and impact of these products is occurring on an international level and U.S. efforts should coincide with these efforts. For example, WHO has convened a Study Group on Tobacco Regulation to produce documents that describe principles and provide guidelines for implementing articles of the WHO Framework Convention on Tobacco Control that are associated with tobacco product testing (Articles 9 and 10). One of the documents, "Guiding Principles for the Development of Tobacco Product Research and Testing Capacity and Proposed Protocols for the Initiation of Tobacco Product Testing"[94] provides guidelines for the testing and assessment and for the regulation of contents and emissions from tobacco products. A long-term vision and direction for tobacco control as well as coordinated and complimentary activities amongst organizations, tobacco-control advocates, policy makers, and researchers are critical at this juncture in tobacco control.

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Effect of Smokeless Tobacco Product Marketing and Use on Population Harm from Tobacco Use
Policy Perspective for Tobacco-Risk Reduction

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Abstract: This article presents policy perspectives on the marketing of smokeless tobacco products to reduce population harm from tobacco use. Despite consensus that smokeless tobacco products as sold in the United States are less dangerous than cigarettes, there is no consensus on how to proceed. Diverse factions have different policy concerns. While the tobacco industry is exempted from U.S. Food and Drug Administration (FDA) oversight, the pharmaceutical industry whose nicotine replacement therapy (NRT) medicines compete with smokeless tobacco as noncombustible nicotine-delivery systems are regulated by the FDA. Some public health experts support smokeless tobacco use to reduce population harm from tobacco; other public health experts oppose promoting smokeless tobacco for harm reduction. Adult consumers can freely purchase currently-marketed smokeless tobacco products and even more-deadly cigarettes.

Concerns with and advantages of smokeless tobacco products are discussed. In that noncombustible medicinal nicotine-delivery systems have been proven to be effective smoking-cessation aids, smokeless tobacco, as another source of psychoactive doses of nicotine, could be used similarly, in a dose–response fashion as a smoking-cessation aid (consistent with FDA principles for evaluating generic versions of drugs). Price measures should be used on tobacco products to make costs to consumers proportional to product health risks (which would make smokeless tobacco much cheaper than cigarettes), and smokeless tobacco should be encouraged as an option for smoking cessation in adult smokers, particularly for those who have failed to stop smoking using NRT or other methods.
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D espite considerable scientific consensus that smokeless tobacco products as sold in the United States, although not safe, are less dangerous than cigarettes to physical health,[1] there has been fractious dissension within tobacco control, sometimes bitter and personal, on whether smokeless tobacco can be or should be used to help reduce population tobacco harm. Even if disagreed with, the perspectives reviewed here will hopefully enrich arguments and move thinking forward in this contentious area.

The Product

Fundamental to the four P's of marketing (product, placement, promotion, and price) is the product itself.[2] Some smokeless tobacco products (e.g., chewing tobacco and moist snuff) are known to stimulate saliva and result in spitting. Some newer, pressed, smokeless tobacco products do not promote spitting; and some are taken into the nose. While some smokeless tobacco products as used in the U.S. today are probably more dangerous than others, this review will not evaluate that evidence.[3] Smokeless tobacco products do not directly expose the lungs to tobacco toxins and do not deliver toxins to the lungs of passive (secondhand) smokers. Cigarettes are dominant causes of lung cancer, chronic obstructive pulmonary disease (COPD), and heart disease, while smokeless tobacco is very unlikely to be a cause of lung cancer or COPD, and probably a lesser cause of heart disease and oral cancer than cigarettes.[3–8] A Royal College of Physician's Committee concluded that smokeless tobacco was "10–1000 times less hazardous than smoking depending on the product,"[9] and clearly a lower-risk product than cigarettes.

Multiple Factions with Different Perspectives

Table 1 offers an outline of the major factions involved with smokeless tobacco marketing and policy in the U.S. and elsewhere. Juxtaposing these factions shows a complex system in which one faction's interests and

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Table 1. Overview of parallel factions involved in smokeless tobacco product marketing

Faction	A key function	Selected current marketing and policy status in the U.S.	Selected current marketing and policy status elsewhere in the world
Tobacco industry (smokeless)	Sell tobacco products	Can market to adults as long as they avoid explicit health claims (e.g., cannot say smokeless tobacco is an effective smoking-cessation aid or is lower risk to health than cigarettes); Congressional health warnings are on product and advertising.	Moist snuff (literally suckable tobacco) is banned in most of the EU
Pharmaceutical industry	Sell medicines	For prescription smoking-cessation aids, medical permission, and oversight; for OTC products, FDA-approved, with cautions and instructions. Selective marketing of prescription products; widespread marketing of OTC products for smoking cessation only, yet OTC products can be used in many ways by consumers.	In Austria, Brazil, Canada, France, Norway, Portugal, and Venezuela have "temporary abstinence" (i.e., temporarily abstaining from cigarettes in situations where smoking is prohibited) as an approved indication for NRT[10]
Consumers	Buy or not	Consumers can in practice do whatever they choose with any OTC medicine or tobacco product available; prescription medicines subject to greater restrictions on consumers. For example, consumers can use smokeless tobacco as a temporary substitute for cigarettes or a permanent substitute for cigarettes or a multiweek smoking-cessation aid (as indicated for NRT).	Many EU smokers do not have the option of buying moist snuff. Sweden is an exception where moist snuff has become popular among men.
Public health workers—anti-tobacco and anti-tobacco-caused disease	Protect and promote health	These workers promote never using or ceasing use of all tobacco products and vary in their level of support for nicotine-based medicines for cessation.	Same as in the U.S.
Public health workers—anti-tobacco-caused disease (harm reduction)	Protect and promote health	These workers promote never using or ceasing use of all tobacco products and, for those who do use tobacco, the use of lower-risk nicotine-delivery systems (including smokeless tobacco) as ongoing substitutes for cigarettes (i.e., as smoking-cessation aids).	Same as in the U.S.

EU, European Union; FDA, Federal Trade Commission; NRT, nicotine replacement therapy; OTC, over-the-counter.

regulatory concerns may be irrelevant to another faction. The table includes two divergent public health approaches, each striving to improve public health, but also seeing somewhat different strategies as apt. Consumers, the tobacco industry, and the pharmaceutical industry are also important factions. The pharmaceutical industry is included because it is part of the countermarketing efforts against cigarettes and nicotine replacement therapy (NRT) medicines and smokeless tobacco products can be viewed as competing products. Notwithstanding the different goals and standards of the pharmaceutical and tobacco industries, NRT and smokeless tobacco are both effective, noncombustible nicotine-delivery systems. The example in Table 1 from elsewhere in the world indicates interestingly discrepant policies.[10] While the U.S. has not formally approved use of NRT for temporary abstinence from cigarettes, such a use has been approved by authorities elsewhere in the world and happens to be identical to current uses promoted by the tobacco industry for smokeless tobacco in the U.S. (for "when you can't smoke").[11]

Smokeless Tobacco Products Have Been and Are Being Sold in the U.S.

The U.S. Food and Drug Administration (FDA) does not presently regulate tobacco-based nicotine-delivery systems (cigarettes, cigars, smokeless tobacco). Smokeless tobacco products are advertised legally and sold widely to adults (and sometimes illegally to children). That pharmacologically active tobacco products are exempted from FDA regulation—as are, to some extent, widely sold pharmacologically-active herbal and food supplement products—should make us aware that, for some people, many of the drugs they take are not FDA-approved.[12]

Evidence that Smokeless Tobacco Is an Effective Cigarette Substitute and Cessation Aid

Popular forms of tobacco products deliver adequate doses of nicotine to the brains of users, stimulate the chemical senses (taste and smell), and are reasonably convenient to use.[13] "Convenience" refers to many

issues: for example, cigarettes are inconvenient and smokeless tobacco products convenient in highly flammable environments. Depending on the historic period and place, popular tobacco products have been smoked (either inhaled into the lungs or just puffed into the mouth), chewed, sucked, or snorted.[13] Demographic patterns of use have varied. In some times and in some places, men have been nearly exclusive users of a given product; and in other times and other places, women have resembled men in use of the same product.[14] When smokeless tobacco became inconvenient to use in the late 1800s, because public spitting was outlawed (out of concern about the spread of disease), this dominant form of tobacco use decreased in popularity.[13] Similarly, health-related bans of indoor smoking have been associated with declines in the popularity of cigarette smoking in the U.S.[15,16] In neither case did the pharmacokinetics of smokeless tobacco or cigarettes change, rather it was the prevailing cultural context for the use of the product that changed. Note that smokeless tobacco was by far the most popular form of tobacco use in the early 19th century in the U.S.[17] Up until the mid-1920s in the U.S., more smokeless tobacco than cigarettes (both measured in pounds) were sold per capita.[18]

Smokeless tobacco use was observed by the first Europeans in the Americas. Amerigo Vespucci published the first printed account of tobacco use in 1505, focusing on the use of smokeless tobacco, ". . . which they chewed like cattle to such an extent that they could scarcely talk . . . ."[19] Dickson also commented: ". . . . certainly sailors have always chewed [tobacco] from the time of their landing on American soil up to the present."[19] Interestingly, the observation by Dr. Claes Lundgren in the 1960s of Swedish submariners using smokeless tobacco to cope when unable to smoke cigarettes led to the development of NRT (Nicorette®) as a smoking-cessation aid.[20]

Smokeless tobacco was used as a smoking substitute by Catholic priests in Europe in the 1600s when forbidden to smoke.[21] In workplaces where smoking was not allowed, smokeless tobacco was used as a substitute for smoking and sometimes as a preferred form of tobacco use both at work and when not at work—in mines, in sawmills, in munitions plants, and by soldiers in the field when smoking was impractical.[17]

Pharmacologic research has produced consistent evidence that smokeless tobacco is addictive (because it is a significant source of nicotine[4–6]). Cigarettes and smokeless tobacco products both have been described as "highly engineered, drug delivery devices" that produce user-controllable and addictive doses of nicotine.[22] Smokeless tobacco provides plasma nicotine levels that are similar to those from cigarettes.[23,24] Smokeless tobacco users have been found to exhibit withdrawal symptoms when abstaining from smokeless tobacco.[24] Medicinal nicotine in general has not shown

great success in treating smokeless tobacco dependence,[25] but consistent with the high levels of nicotine delivered by smokeless tobacco, when high doses of medicinal nicotine are given, promising results have been found.[26] One direct study of smokeless tobacco as a smoking-cessation product has found encouraging results, indicating a key nicotine-based action.[27]

Smokeless tobacco and smoking trends in Sweden have been the object of much attention,[28–34] including evidence from Sweden that increased smokeless tobacco use was related to declines in daily smoking prevalence.[28,29,32] Interpreting societal trends is challenging. Even if smokeless tobacco caused some of the drop in daily smoking among males in Sweden, this does not guarantee that the same would happen in the U.S.[30] One econometric study supports that smokeless nicotine (in the form of NRT) is cross-elastic with cigarettes[35]; another study shows the same pattern for smokeless tobacco and cigarettes.[36] In other words, increased cigarette prices are associated with increased use of smokeless tobacco as well as with increased use of NRT. This is evidence for nicotine-based substitutability.

The FDA procedures for approving generic versions of pharmaceuticals offer support for smokeless tobacco as a smoking substitute and cessation aid.[37] In addition to the issue of safety, a key issue is the evaluation of generic drugs for "bioequivalence," that is, does the new product deliver necessary doses of active ingredients. A tobacco company could likely engineer a smokeless tobacco product with similar pharmacokinetics to, for example, the Commit® (GlaxoSmithKline, Philadelphia PA) nicotine lozenge. If the pharmacokinetics indicated bioequivalence, since many placebo-controlled trials have established that nicotine is the active ingredient of smoking-cessation aids, there would be no requirement to repeat the trials with smokeless tobacco. Considering FDA rules for generic drugs, a smokeless tobacco product might be approvable, because of existing evidence on NRT, as an effective smoking-cessation aid, but it might not be marketable largely because of safety concerns, or marketed as a prescription-only product. FDA's regulatory power may be viewed as most determining of product use when it serves to keep the product off the market completely. Given that smokeless tobacco is already available, consumers could in practice so use the product—without FDA approval of such use.

Smokeless tobacco products have been promoted in the U.S. as cigarette substitutes (for use when one cannot smoke),[11] but not as smoking-cessation aids, probably because tobacco products are exempted from FDA regulation. A major tobacco company would be unlikely to apply for smokeless tobacco to be marketed in direct competition with FDA-approved NRT. Applying for FDA approval could risk placing manufacturers under a new regulatory jurisdiction, possibly leading to

FDA regulation of all smokeless tobacco products. Such regulatory/policy issues do not nullify that, if submitted to the FDA as a smoking-cessation aid, the FDA likely would need to judge them as effective, but not necessarily safe.

Consumer Preferences

Even very similar consumer products (e.g., Coke® vs Pepsi®) are subject to complex and strong consumer preferences.[38] Many features can be distinguished between NRTs and smokeless tobacco products: cost, likely addictiveness, taste, and health risks; but they are nevertheless functionally similar as noncombustible, effective nicotine-delivery systems with potentially similar uses. One recent study has found that many, but not all, cigarette smokers preferred Commit lozenge to smokeless tobacco, based on descriptions of the products.[39] But, users of a strong moist snuff were found to much prefer that product to the Commit lozenge or to new compressed smokeless tobacco products.[40] To quit smoking cigarettes, some consumers would prefer to use smokeless tobacco, some nicotine gum, some the patch, and some no drug products.[41] Such choices often are not a matter of efficacy, but of consumer preference. Consumer acceptability should not be confused with whether a product works. If one accepts that smokeless tobacco can work to help smoking cessation, the remaining issues include who might use it, when it might be used, and should these individuals have selected another way to quit smoking out of concern for safety? Concerning overall risk reduction, consumers should be encouraged by health professionals to prefer NRT to any smokeless tobacco product, as a substitute for smoking or as a smoking-cessation aid.[33,42,43] Several potential issues such as product cost (especially per mg of nicotine delivered[44]), taste, effectiveness, and image, could lead some consumers to prefer smokeless tobacco products to NRT. Most NRT sold in the U.S. is now available without prescription, and, in effect, consumers are essentially free to use it however they prefer.[43]

Counter-Marketing of Cigarettes

The World Bank did an evidence-based review of the counter-marketing of cigarettes and concluded that price measures (e.g., higher cigarette taxes) were the most effective measure to reduce smoking. Several nonprice measures also helped to reduce smoking: consumer information, research, cigarette advertising and promotion bans, warning labels, and restrictions on public smoking. Increased access to NRT and other cessation strategies were also recommended.[45] With respect to smokeless tobacco policy, two modifications of the World Bank position should be considered.

More-Dangerous Tobacco Products Should Be Proportionately More Expensive to Purchase

Steps should be taken to ensure that more-dangerous tobacco products (especially cigarettes) are the more-expensive tobacco products. This is not fundamentally a new proposal. In 1962, the Royal College of Physicians recommended differential taxation with cigars and pipes being taxed less than cigarettes.[46] The econometric literature on tobacco taxation supports the general finding of substitutability of tobacco products, with higher cost related to reduced consumption of a given product.[35,36,47] The pattern of results has led to the recommendation that differential taxation as a function of harm is an important aspect of differential taxation.[48] This process probably should not start with the current price of cigarettes and work down to cheaper and cheaper products, rather it would be desirable to make cigarettes very expensive (for example, several times the cost of NRT) and then start reducing the cost of other tobacco products in some way proportionate to disease risks. Such a differential taxation plan is part of the likely best strategy for reducing cigarette use; if smokeless tobacco costs the same or is more expensive, it could undermine the effects of tax increases on cigarette use, because of product substitutability.[48]

Smokeless Tobacco Should Be Treated As an Alternative Smoking-Cessation Aid

Lower-cost NRT can promote smoking cessation[35] and, presumably,[47] promote NRT to be preferred to smokeless tobacco, therefore efforts should be made to have NRT cost significantly less than smokeless tobacco. As smokeless tobacco products can be effective smoking-cessation aids and may be able to function as useful alternatives to NRTs for those who prefer not to use NRTs (see discussion above on both points), then smokeless tobacco could be used as another tool to promote smoking cessation.[49] It also would be good to encourage the development of more consumer-attractive NRTs, that could be preferred to smokeless tobacco products.[33,42,43] While solely promoting smokeless tobacco as a way to quit smoking would be likeliest to minimize adverse effects of smokeless tobacco marketing, it is unlikely to happen for the policy reasons indicated above. Health professionals should be willing to turn to suggesting smokeless tobacco as a smoking-cessation aid when NRT and other treatment aids and efforts have failed.

Concerns About Marketing Smokeless Tobacco As a Substitute for Cigarettes

The objections to claims of the public health value of the lower risk to individual users of smokeless tobacco

are generally of three interrelated types. Each type can be viewed as a form of "slippery slope" argument, holding that this first reduced-risk step may lead ultimately to greater risk overall. Slippery slope arguments are not considered strong logical arguments, and their force depends on sound and detailed analysis of what might happen, along with consideration of the likelihoods of such ill effects.[50] In other words, the specter of "what might happen" is not a convincing argument on its own. There needs to be an assessment of the likelihood of ill effects.

Research Is Needed on Health Risks of Smokers Switching to Smokeless Tobacco Products

One critique notes there is little research on the risk levels of various patterns of dual use of smokeless tobacco and cigarettes.[51] While strictly true, it is also true that well-established dose–response principles should apply. Sequential "dual" use (moving completely off cigarettes to smokeless tobacco) will probably show reduction in smoking-caused diseases—as a function of duration of smoking and daily dose of smoking. Substituting only a few cigarettes a day with smokeless tobacco is unlikely to reduce significantly tobacco harm. The longer and more one has smoked, the less likely a reduction in smoking-caused diseases will take place. For some problems the health damage may already have been done (e.g., cancer), and it will take years for the problem to appear, even if the individual has stopped all tobacco use. For concurrent dual use of NRT and cigarettes in smokers who do not want to quit smoking, because nicotine intake is somewhat regulated, total intake of smoke toxins is unlikely to rise with dual use and will likely decrease.[52] The greater the reduction in smoke toxins, the greater the reduction in smoke-caused diseases. While limited studies demonstrate this risk-reduction at present, it is also true that the current health risks of cigarette smoking are an urgent public health problem.

Risk of Increased Use and Increased Users of Tobacco Products

A second critique has been described by Hatsukami et al.[51]: "Aggressive marketing of smokeless tobacco as less-risky than cigarettes may not necessarily lead to reduced total tobacco use but increased use, especially newly initiated use." Converting those who would have been nontobacco users without smokeless tobacco to any tobacco use would be a concern. The focus, from one public health perspective, should be on reducing total tobacco-related disease, not the total number of tobacco users. Of course, a lower-risk product could increase population risks, but as a function of the increase in use and the decrease in danger from the product. Even though smokeless tobacco is less danger-

ous than cigarettes to individual users, if many more people start using the product, is it likely to produce a net loss for public health? This has become a frequent question when considering the population effects of less-dangerous products for individuals. To get a sense of scale for the possible problems caused by increased use of a less-dangerous product, consider the risk/use equilibrium, an equilibrium achieved by increasing use as risk decreases.[53] If the level of use increases faster than risk is decreased, public health would be hurt. If risk levels are decreased faster than use rises, public health would be helped. Smokeless tobacco products appear to be very unlikely to increase harm to public health if they are substituted for cigarettes, because the risk reduction to individual users is large. For example, for a product that is 95% less dangerous than cigarettes, an impossible 400% of the population (i.e., 20 times greater) would need to use the product to equal the early death from smoking (assuming 20% of the population smoking to begin with). For a product that is 80% less dangerous than cigarettes, an impossible 100% of the population (i.e., 5 times greater) would need to use the product to equal the early death from smoking (i.e., from 20% of the population smoking). It is doubtful that close to 100% of the population would come to use any tobacco product. If smokeless tobacco is used to help cope with smoking restrictions, while the individual continues to be a cigarette smoker, this would be an example of a lower-risk product contributing to the ongoing use of a higher-risk product. This problem could arise from the use of either NRT or smokeless tobacco as a temporary substitute for cigarettes, but there is little evidence to date that such problems have been important.

Gateway Fears

The third common critique arises from concerns that smokeless tobacco may cause subsequent cigarette smoking and hence the reduced risk is only temporary,[51,54,55] but other experts have found evidence inconsistent with a causal gateway,[56–59] and have argued that smokeless tobacco may even act to prevent cigarette smoking in high-risk youth and that much of the association between smokeless tobacco and smoking is not causally linked. Counter-marketing and other prevention efforts to reduce cigarette smoking should be able to decrease the possible progression from smokeless tobacco to cigarettes. In a world where cigarettes are much more expensive than and recognized as much more dangerous than smokeless tobacco, the gateway should swing more toward the less-dangerous product than toward the more-dangerous product.

Unfortunately, inaccurate information that smokeless tobacco is just as dangerous as or even more dangerous than cigarettes has been widely promoted.[60,61] A formal complaint under the Data Quality Act resulted in the

National Institute of Aging changing the information on its website on smokeless tobacco.[62] One analysis concluded that overall there was a "misleading and harmful public message about smokeless tobacco" to be found on the Internet.[61] There have since been recent improvements in the quality of health information on smokeless tobacco.[63]

Health communications should do more than simply inform that "there is no safe tobacco product."[64] The Congressionally-mandated rotating warning that "WARNING: This product is not a safe alternative to cigarettes" is in effect a "not safe" message. While this message is true, it is also a truism, in that "nothing is completely safe," and it is of limited value in that the public largely knows that there is no safe tobacco product.[64] One of the lessons of the low-tar-cigarette disaster is that, while the public understood that "low-tar" cigarettes were not safe, a public health tragedy resulted from the simultaneous and nonparadoxic belief that low-tar cigarettes were "safer."[65]

Can, Will, or Should Smokeless Tobacco Marketing Be Used As Part of a Comprehensive Tobacco-Control Plan?

The reviewed evidence indicates that smokeless tobacco products as effective nicotine-delivery systems can function as cigarette substitutes and cessation aids. As with other consumer drug products, smokeless tobacco will be acceptable to some consumers and not to others as a function of both pharmacologic and non-pharmacologic factors.

Whether smokeless tobacco products will be substituted for cigarettes in the U.S. will likely depend on the entire pattern of comprehensive tobacco-control measures (including taxation, health information, smoking restrictions) and concerns about net population harm that might be the result of doing anything other than discouraging any smokeless tobacco use. Of course, not all possible adverse effects of any encouragement or opportunities to substitute smokeless tobacco for cigarettes have been reviewed and discussed here. The issue of moral hazard related to public health measures can be very complex; for example, it has been found that increased promotion of NRT—generally viewed as good for tobacco control—is associated with small increases in the number of cigarettes smoked per day by young smokers, perhaps because smokers know they have a way to stop when they desire to do so.[66] They estimated that if NRT advertising were eliminated, youth smoking would decrease from "5.77 cigarettes per day to about 5.27, or less, cigarettes per day."[66] Another question not discussed is will former smokers be attracted back to tobacco use with the availability of safer, lower-cost smokeless tobacco? Consequentialist (ends-based) moral philosophies are often challenged by the impracticality of a complete analysis of all possible costs and benefits of any action.[67] It is important to remember that smokeless tobacco is not essentially a new product. The longstanding, current, and legal availability of smokeless tobacco products gives some reason to believe that those who like smoking cigarettes will not readily come to prefer smokeless tobacco; if it were such an "easy sell," the fears of cigarette smoking as a deadly product as well as bans on indoor smoking probably would have caused already a greater switch to smokeless tobacco or NRT. (The switch from high-yield cigarettes to misleading "low-yield" cigarettes is a switch from one cigarette to another, not a switch to an entirely different type of product.) Many smokers do quit without the use of any type of pharmacologic cessation aid.[5]

Should smokeless tobacco play a role in comprehensive tobacco control? This is both an ethical and a practical question. The Royal College of Physicians recently concluded, after a detailed bio-ethical analysis, that a comprehensive plan to discourage cigarette smoking (including pricing, marketing, and regulatory controls) should make alternatives to smoking tobacco more widely available.[68] Econometric research indicates that if one desires the maximum reduction in cigarette sales with a tax increase on cigarettes, it is also important to make other substitutable nicotine-delivery systems (NRT and smokeless tobacco) cost less than cigarettes.[48]

Currently, proposed legislation on the regulation of tobacco products by the FDA may bring about little to no change in traditional tobacco products.[69] Any proposed legislation probably should attend to the inter-relationships among nicotine-delivery products as a complex system, rather than focus so much on the control of claims about products. Manufacturers could avoid any cumbersome evaluation process involved with justifying claims for new products by simply focusing on making their billions on the sales of traditional tobacco products. Differentiating traditional nicotine-delivery systems in terms of knowledge of risks, price, and availability should be part of a comprehensive tobacco-control program, especially in a country where smokeless tobacco and deadly cigarette products are and will likely be widely available.

Despite scientific consensus that smokeless tobacco products as sold in the U.S. are much less dangerous to the health of users than are cigarettes, there remains no consensus on whether widely available smokeless tobacco can be or should be used to help reduce population tobacco harm. Research agendas have been proposed,[1,6,8] but there will still be disputes about how many answers or terms are needed before action steps can be supported.[51] The Precautionary Principle encourages us to be "better safe than sorry,"[70] and it can seem to be a public health virtue. This principle may be misapplied[71] on this issue, but nevertheless it is being

applied. Saner has argued: "If precaution is one-sided (only considering the risk of commission, i.e., doing an action), then it can become an antinovelty principle."[72] Overemphasis on precaution is not necessarily a public health virtue in the face of an existing public health crisis—the legal and widespread marketing and sale of deadly cigarettes. [73]

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Epidemiologic Perspectives on Smokeless Tobacco Marketing and Population Harm

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Abstract: Moist snuff is the most popular form of orally-used smokeless tobacco in North America and parts of Europe. Because moist snuff use conveys lower risks for morbidity or mortality than does cigarette smoking, its use has been proposed as a tobacco harm–reduction strategy. This article critically reviews new and published epidemiologic evidence on health effects of moist snuff and its patterns of use relative to smoking in the United States, Sweden, and Norway. The available evidence suggests that: (1) moist snuff is a human carcinogen and toxin, (2) increased promotion of moist snuff has led to increased sales in those countries, (3) the uptake of moist snuff in these three countries during the past several decades has occurred primarily among adolescent and young adult men, (4) increased prevalence of snuff use has not been associated consistently with a reduction in smoking initiation or prevalence, (5) moist snuff use apparently plays a very minor role in smoking cessation in the U.S. and an inconsistent role in Sweden, (6) U.S. states with the lowest smoking prevalence also tend to have the lowest prevalence of snuff use, (7) there are no data on the efficacy of snuff as a smoking-cessation method, (8) the prevalence of cigarette smoking is relatively high among people who use snuff, and (9) snuff use is more consistently associated with partial substitution for smoking than with complete substitution. The evidence base for promotion of snuff use as a public health strategy is weak and inconsistent.
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Introduction

One session in the National Institutes of Health (NIH) State-of-the-Science Conference on Tobacco Use: Prevention, Cessation, and Control asked the four invited panelists, "What is the effect of smokeless tobacco product marketing on population harm from tobacco use?" This article summarizes the available epidemiologic data to answer that question.

Hundreds of millions of people worldwide are addicted to smokeless tobacco, and use by young people is increasing in many countries.[1] The types of product vary widely around the world. The common defining characteristics of smokeless tobacco products are that they are not burned by the consumer at the time they are used, they deliver nicotine into venous circulation through passive absorption across oral or nasal mucosa, and virtually all products contain human carcinogens and toxins at levels substantially higher than are typically found in any nontobacco consumer product.[1] There does appear to be a range in levels of carcinogens and toxins among the various American and Swedish moist snuff products, as discussed elsewhere in this supplement.[2]

There has been recent discussion within the tobacco-control community concerning the role, feasibility, and supporting evidence of a harm-decreasing strategy, through promotion of smokeless tobacco products, in reducing the societal burden of tobacco use.[3] Because of lower risks for morbidity or mortality compared with cigarettes, various smokeless tobacco products, particularly moist snuff, have been suggested as potential reduced-exposure products for smokers who are unable or unwilling to quit using tobacco.[4–6] Smokeless tobacco manufacturers have used that rationale in advocating and lobbying for regulatory changes in many countries.[7–9]

The objectives of this review are: (1) to briefly review the epidemiologic evidence for smokeless tobacco and disease, (2) to review the available epidemiologic data on patterns of smokeless tobacco usage and consumption relative to cigarette smoking, and (3) to discuss the implications of these data.

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Health Effects

Compared with the large body of literature on the adverse health effects of cigarette smoking, the literature on adverse health effects associated with smokeless tobacco use is far smaller and, for some disease end-

points, less conclusive. In part, that limitation reflects the nature of smokeless tobacco use in most parts of the world. In general, smokeless tobacco use is far less prevalent than smoking in most developed nations, so observational studies that include an adequate sample size of exposed people are more difficult to assemble. In addition, a large proportion of smokeless tobacco users in most countries also have a history of using burned types of tobacco products such as cigarettes, bidis, or hookahs, a factor that creates challenges in identifying cohorts whose only form of tobacco use is smokeless tobacco.

There have been several large comprehensive reviews on the health effects of smokeless tobacco, so this article will not review most of the original studies in detail. Instead, it will summarize the conclusions of those reviews where possible.

Cancer

A working group convened by the International Agency for Research on Cancer (IARC) in 1984 reviewed the available epidemiologic, animal, and chemical literature to reach a determination on the carcinogenicity of smokeless tobacco.[10] The working group concluded: "There is sufficient evidence that oral use of snuffs of the types commonly used in North America and Western Europe is carcinogenic to humans." The review also concluded: "There is limited evidence that chewing tobacco of the types commonly used in these areas is carcinogenic" and "Epidemiologic studies that did not distinguish between chewing tobacco and snuff provide sufficient evidence for the carcinogenicity of oral use of smokeless tobacco products, as reported in these studies." That working group summarized the findings as: "In aggregate, there is sufficient evidence that oral use of smokeless tobacco of the above types is carcinogenic to humans."

The question of carcinogenicity of smokeless tobacco products was revisited by the IARC in 2004, when it convened another working group to conduct a comprehensive review and evaluate the evidence. A summary of the review has been published,[11] but as of January 24, 2007, the full report has not yet been issued. The working group concluded that smokeless tobacco is "carcinogenic to humans." More specifically, the group concluded: "Overall, there is sufficient evidence that smokeless tobacco causes oral cancer and pancreatic cancer in humans, and sufficient evidence of carcinogenicity from animal studies." The working group also evaluated the evidence for carcinogenicity of two tobacco-specific N-nitrosamines, N'-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), which are the most abundant strong carcinogens in smokeless tobacco. The group concluded that exposure to NNN and NNK is "carcinogenic to humans," on the basis of sufficient evidence

from animals and strong mechanistic evidence in exposed humans.

The carcinogenicity of smokeless tobacco was also evaluated by an advisory committee to the U.S. Surgeon General in 1986.[12] That review concluded: "The scientific evidence is strong that the use of snuff can cause cancer in humans."

Critchley and Unal[13] conducted a comprehensive review of the health effects of smokeless tobacco and concluded that there is a substantial risk of oral cancers associated with the types of smokeless tobacco used in India. Furthermore, they concluded that "most recent studies from the U.S. and Scandinavia are not statistically significant, but moderate positive associations cannot be ruled out due to lack of power."

Rodu and Cole[14] conducted a review of 21 published epidemiologic studies on use of American or Swedish smokeless tobacco and the risk of cancers of the upper respiratory tract, and calculated summary relative risks by product type. The authors concluded that the lowest estimated relative risks (RRs) were found among users of chewing tobacco (0.6–1.7) and among users of moist snuff (0.7–1.2). They concluded that users of dry snuff have higher risks, with RRs from about 4 to 15. RRs for upper respiratory tract cancers were considered intermediate for unspecified type of smokeless tobacco used, speculating that it possibly reflected use of either the lower- or higher-risk products among different individuals. However, the conclusions were heavily influenced by the classification of the landmark case–control study by Winn et al.[15] as a study of dry snuff. Winn et al. reported an estimated RR of 4.0 for snuff use and oral cancer, but that article did not specify whether study participants used dry or moist snuff. Laboratory assays conducted in the 1980s found no significant differences between moist snuff and dry snuff in the levels of carcinogenic tobacco-specific N-nitrosamines, suggesting those products carried comparable carcinogenic potential.[16]

Cardiovascular Diseases

A systematic review of smokeless tobacco and cardiovascular diseases published several years ago[17] included just one cohort study[18] and two case–control studies.[19,20] The large prospective cohort study found a 40% excess risk of cardiovascular mortality among smokeless tobacco users,[18] but the two case–control studies found no association between smokeless tobacco use and myocardial infarction. Critchley and Unal[17] concluded there may be an association between smokeless tobacco use and cardiovascular disease, but further rigorous studies with adequate sample sizes are required to reach a more definitive determination. Since that review was published, two large prospective cohort studies[21] and a large international case–control study[22] have been reported. Henley et al.[21] studied the

association between smokeless tobacco use and mortality among men enrolled in Cancer Prevention Study I (CPS-I) in 1959 or Cancer Prevention Study II (CPS-II) in 1982. Men who currently used snuff or chewing tobacco at baseline had higher death rates from cardiovascular diseases than men who did not in both CPS-I (hazard ratio [HR]=1.18; 95% confidence interval [CI]=1.11–1.26) and CPS-II (HR=1.23; 95% CI=1.09–1.39). All analyses excluded men who reported current or former smoking of cigarettes, cigars, or pipes. In both cohorts, current smokeless tobacco use was significantly associated with death from coronary heart disease or stroke. A large international case–control study[22] found a significantly elevated risk for myocardial infarction associated with smokeless tobacco use among subjects with no history of using other tobacco products (odds ratio [OR]=2.23; 95% CI=1.41–3.52), which was only slightly lower than the risk associated with smoking (OR=2.95; 95% CI=2.77–3.14). One Swedish case–control study found no association between snuff use and stroke,[23] although just 42 subjects of the 827 in the study were snuff users with no history of cigarette smoking.

Reproductive Health Effects

There is evidence that smokeless tobacco use increases the risk for adverse reproductive health outcomes among pregnant women. An Indian prospective cohort study of more than 1100 pregnant women found an increased risk for low birthweight (OR=1.6; 95% CI=1.1–2.4); preterm delivery at <37 weeks (OR=1.4; 95% CI=1.0–2.1), <32 weeks (OR=4.9; 95% CI=2.1–11.8) or <28 weeks (OR=8.0; 95% CI=2.6–27.2); and stillbirth (HR=2.6; 95% CI=1.4–4.8).[24,25] Consistent with that study, a Swedish cohort study[26] found an increased risk for preterm delivery (OR=1.98; 95% CI=1.46–2.68) associated with snuff use by pregnant women, which was greater than that associated with cigarette smoking (OR=1.57; 95% CI=1.38–1.80). Snuff use was also associated with a significantly increased risk for pre-eclampsia (OR=1.58; 95% CI=1.09–2.27), which also was higher than the risk for pre-eclampsia associated with smoking (OR=0.63; 95% CI=0.53–0.75). A cohort study conducted in South Africa found that women who used snuff during pregnancy had a significantly shorter mean gestational age (37.9 [±1.4] weeks) than those who smoked (38.7 [±2.4] weeks) or did not use tobacco (38.3 [±1.5] weeks) during pregnancy.[27]

Oral Health Effects

Oral health effects of smokeless tobacco use include localized gingival recession,[28–34] oral soft tissue lesions,[31,33–50] and possibly dental abrasion.[51–55] There is some evidence that U.S. chewing tobacco may increase the risk for dental caries,[56] but there are relatively few studies of smokeless tobacco and dental caries and the findings are inconsistent.[30,33,57–61] A few studies suggest that smokeless tobacco use may be a risk factor for periodontitis.[62,63]

Nicotine Addiction

All forms of oral smokeless tobacco are capable of delivering nicotine by absorption through the oral mucosa, into venous circulation, and to receptors in the central nervous system.[64] There is compelling evidence that smokeless tobacco use can result in nicotine addiction.[12,65,66]

Comparative Mortality Risks for Cigarettes and Smokeless Tobacco

There is overwhelming consensus in the scientific community that cigarette smoking is the leading preventable cause of death in the U.S.[67] and globally.[68] It therefore follows that virtually any consumer product poses a lower risk for premature mortality than does cigarette smoking.

There are few cohort studies that directly compared the overall risk for death associated with western types of smokeless tobacco and cigarettes. In a large 12-year cohort study of Swedish men, Bolinder et al.[69] found an elevated risk for death due to all causes among smokeless tobacco users (RR=1.4; 95% CI=1.3–1.8). That mortality risk was lower than for men who smoked fewer than 15 cigarettes per day (RR=1.7; 95%CI=1.6–1.9) or those who smoked 15 or more cigarettes per day (RR=2.2; 95% CI=2.0, 2.4). Generally consistent with that, the large prospective cohort studies conducted by the American Cancer Society found that men who currently used snuff or chewing tobacco at baseline had higher death rates from all causes than men who did not in both CPS-I (HR=1.17; 95% CI=1.11–1.23) and CPS-II (HR=1.18; 95% CI=1.08–1.29).[70] Those age-adjusted RR estimates were lower than those associated with cigarette smoking among men in CPS-I (RR=1.7; 95% CI=1.7–1.8) and CPS-II (RR=2.3; 95% CI=2.3–2.4).[71]

The most appropriate research question to consider in the context of current smoking is not whether exclusive smokeless tobacco use conveys lower risks than does smoking, but whether people who switch from cigarettes to smokeless tobacco reduce their risks for death or disease. There are nearly no data on that research question. Just one cohort study examined the risk for death among smokers who switched to smokeless tobacco compared to those who quit all tobacco use.[72] That study found that male "switchers" had a higher rate of death from any cause (HR=1.08; 95% CI=1.01–1.15), lung cancer (HR=1.46; 95% CI=1.24–1.73), coronary heart disease (HR=1.13; 95% CI=1.00–

1.29), and stroke (HR=1.24; 95% CI=1.01–1.53) than men who quit using tobacco entirely.

Possible Mechanisms for Smokeless Tobacco in Reducing Population Harm from Tobacco

Although smokeless tobacco has been established as a class of toxic, carcinogenic, and addictive products, its use has been suggested as a tobacco harm-reduction strategy.[73,74] The underlying rationale for such a recommendation is that these products convey a substantially lower risk from morbidity and mortality than does cigarette smoking, and because of its nicotine delivery properties it could serve as an alternative to cigarettes as a nicotine delivery source. Thus, in theory, smokeless tobacco use could reduce population tobacco harm by: (1) preventing smoking initiation, (2) promoting complete smoking cessation, or (3) serving as a partial replacement for cigarettes among continuing smokers. The epidemiologic evidence for each of the three mechanisms is reviewed below.

Prevention of Smoking Initiation

In nearly all countries, initiation of smoking typically occurs during the adolescent or early adult years; smoking initiation after age 25 years is very uncommon.[75,76] Long-term smoking-cessation rates are relatively low among established smokers under 25 years of age.[77,78] If smokeless tobacco use were preventive for cigarette smoking in a population, several patterns of tobacco usage would be expected: (1) in prospective cohort studies, people who used smokeless would be less likely than those who did not use those products to initiate smoking, after adjusting for established risk factors for smoking initiation; and (2) if smokeless tobacco use increased among people under age 25 in a population, it would be accompanied by a decline in the prevalence of smoking in that age group.

Several prospective cohorts from the U.S. examined smoking initiation rates among young people who used smokeless tobacco at baseline but had not smoked. Two relatively recent cohort studies suggest that the use of smokeless tobacco may be a predictor of subsequent smoking among young men in the U.S. In a cohort study of Air Force recruits with a mean age of 19 years at baseline (N=7865), Haddock and colleagues[79] considered regular smokeless tobacco use to be the use of these products at least once per day. The 1-year outcome measure of smoking was defined in this study as any smoking within the preceding 7 days. Among current smokeless tobacco users, 27% initiated smoking, compared with 26.3% of former smokeless tobacco users and 12.9% of never-users. Adjusting for demographic characteristics, current users (OR=2.33; 95% CI=1.84–2.94) and former users (OR=2.27; 95%

CI=1.64–3.15) were significantly more likely than never-users to initiate smoking. There was no evidence of a protective effect of smokeless tobacco use.

In a 4-year follow-up study of adolescent and young adult men, Tomar[80] examined the relationship between smokeless tobacco use and initiation of smoking. Data were from the 1989 Teenage Attitudes and Practices Survey (TAPS) and its 1993 follow-up on a U.S. nationally representative cohort of 4000 male youth aged 11–19 years at baseline. Young men who were not smokers in 1989 but regularly used smokeless tobacco were more than three times as likely as never-users to be current smokers 4 years later (23.9% vs 7.6%; adjusted OR=3.45; 95% CI=1.84–6.47). More than 80% of baseline current smokers still were smokers 4 years later. In contrast, more than 40% of baseline current regular smokeless tobacco users became smokers, either in addition to or in place of smokeless tobacco use. Another analysis[81] of the TAPS cohort suggested that smokeless tobacco use was no longer a statistically significant predictor of smoking initiation when psychosocial risk factors were included in multiple logistic regression modeling; the adjusted OR of smoking initiation was 1.97 (95% CI=0.69–5.65) for those who reported regular use of smokeless tobacco. Although not a statistically significant predictor of smoking initiation in that analysis, smokeless tobacco use clearly was not preventive against smoking initiation after adjusting for established psychosocial predictors of smoking. Similarly, a recent cohort study of 2100 boys in grades 7 or 9 at baseline found that those who used smokeless tobacco at baseline but had never smoked were significantly more likely than non-users to initiate smoking during the succeeding 2 years (OR=2.55; 95% CI=1.45–4.47), after adjusting for school grade, parental smoking, sibling smoking, close friend smoking, deviant behavior, low school performance, and past-month alcohol consumption.[82] Although the role of smokeless tobacco as an independent risk factor for smoking initiation has been questioned,[81,83–85] there is no evidence from prospective cohort studies of a preventive effect. Swedish cross-sectional studies that suggested a preventive effect of snuff use for subsequent smoking either excluded the birth cohorts most likely to have used snuff during adolescence or young adulthood[85] or ignored the substantial proportion of Swedish men who smoke on a less than daily basis (45% of all current male smokers)[84] in examining the association between snuff use and smoking initiation.

Secular trends in tobacco use among adolescents and young adults in Sweden, Norway, and the U.S. do not support a preventive effect of smokeless tobacco use for cigarette smoking. Official national data from Statistics Sweden suggest that daily snuff use among youth aged 16–24 years has increased over the past 15 years, from 23.0% in 1988–1989 to 26.5% in 2005 among men, and

from 0.6% to 3.9% among women (Figure 1).[86] Current smoking (i.e., daily or occasional) in that age group exhibited an increasing trend line for male youth during that time period and a declining trend line for female youth over the same time period. In 2004–2005, 33.4% of men and 30.2% of women aged 16–24 years in Sweden were current smokers. However, the prevalence of daily smoking was lower for men (9.3%) than for women (13.3%) in that age group. The secular patterns in tobacco use among Swedes aged 16–24 years suggest that snuff may have served as a partial substitute for smoking among men, but had a negligible effect, if any, on smoking initiation rates for either gender.

Consistent with the findings from Sweden, secular trends in tobacco use among young adults aged 16–24-years in Norway provide no evidence of a preventive effect of snuff use for smoking initiation (Figure 2). The prevalence of snuff use more than doubled among young Norwegian men during the past few decades, from 9% in 1985 to more than 21% in 2002 (snuff use is not reported for women in Norway). The prevalence of current smoking also increased among young men during most of that time, from 37% in 1988 to 47% in 1999. Smoking has remained about equally prevalent for men and women aged 16–24 years for most of the past 20 years, although snuff use by young women in Norway is very uncommon[87] and generally is not reported by Statistics Norway.[88] Nearly all adolescents and young adults in Norway who used snuff also were current smokers.[87,89]

Trend data on the use of smokeless tobacco reveal no apparent preventive effect among U.S. high school

Figure 2. Trends in the proportion of people aged 16–24 who used snuff (daily or occasionally) or currently smoked (daily or occasionally), by gender. Norway, 1985–2002. Data from Statistics Norway.

students (Figure 3). Data from the Monitoring the Future[90] study suggest that daily smokeless tobacco use by U.S. high school seniors exhibited a flat to slight upward trend from 6.4% in 1993 to 8.6% in 1997, a time period during which current smoking increased sharply for both male and female high school seniors. Daily smokeless tobacco use by male high school seniors has generally trended downward since 1997, reaching a prevalence of 4.7% in 2005. Current smoking by male high school seniors also declined during that time period, from 37.3% in 1997 to 24.8% in 2005, and declined among female high school seniors from
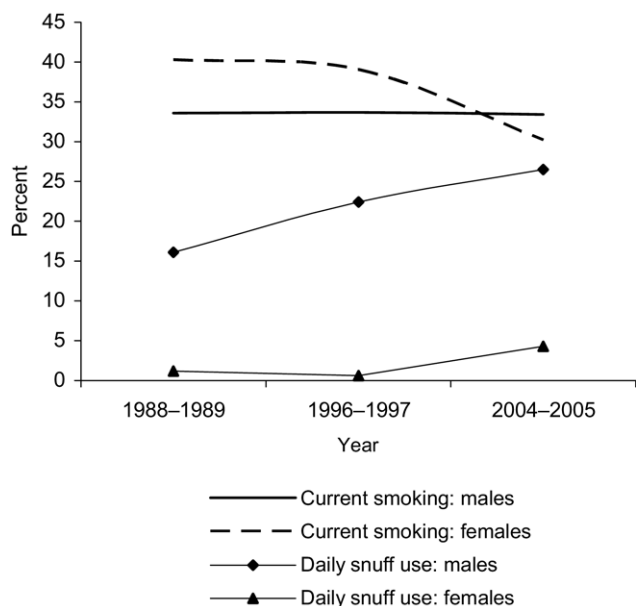
Figure 1. Trends in proportion of people aged 16–24 who used snuff daily or currently smoked (daily or occasionally), by gender. Sweden, 1988–1989 to 2004–2005. Data from Statistics Sweden ULF Surveys.[86]
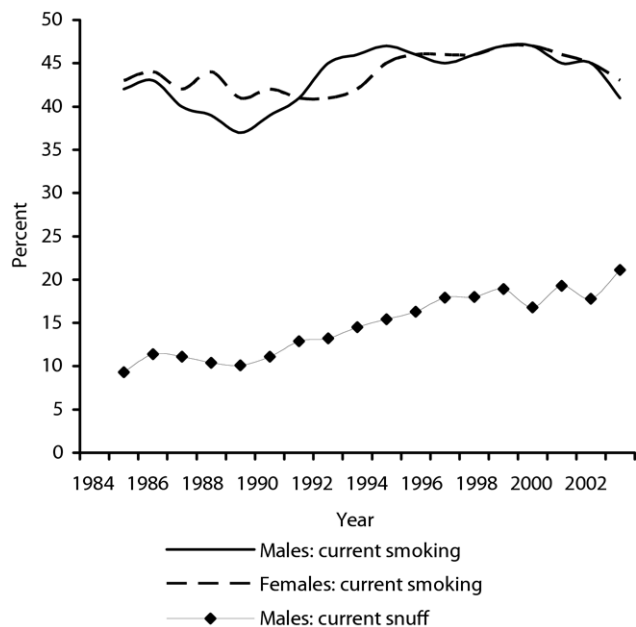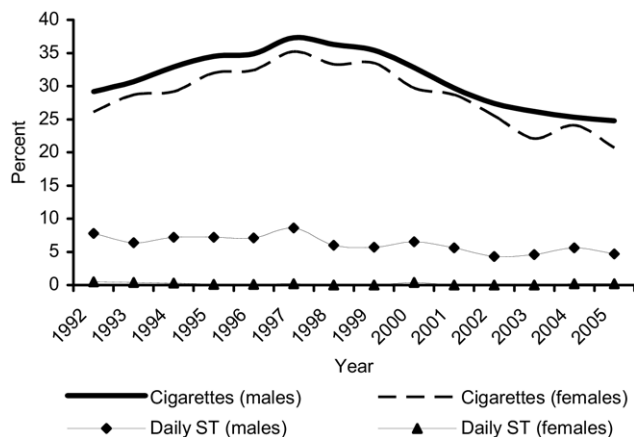
Figure 3. Trends in the proportion of high school seniors who used smokeless tobacco (ST) daily or smoked within the preceding 30 days, by gender. United States, 1992–2005. Data from the Monitoring the Future Project.

35.2% in 1997 to 20.7% in 2005. Daily smokeless tobacco use has remained very rare among female U.S. high school seniors since the Monitoring the Future Project has been tracking smokeless tobacco use, with an estimated prevalence of 0.2% in 2005.

Smokeless Tobacco and Smoking Cessation

If smokeless tobacco use were an effective treatment or substitute for smoking, the expected pattern would be: (1) an increased prevalence of smokeless tobacco use among adults aged 35 years or older would be associated with an increased prevalence of smoking cessation in that age group, (2) a lower prevalence of smoking among states with a higher prevalence of smokeless tobacco use, (3) higher smoking quit rates in the treatment group assigned to use smokeless tobacco than in the control group in randomized controlled trials, and (4) higher smoking quit rates in observational studies that adjusted for relevant correlates of successful quitting such as level of nicotine dependence, stage of readiness to quit, and history of prior quit attempts.

To date, there are no published randomized clinical trials for smokeless tobacco as a smoking-cessation method. Only one published study explicitly examined the effectiveness of snuff use as a smoking-cessation method.[91] That pilot study found that 16 of the 63 subjects (25%) in the study had quit smoking by using snuff at the 1-year follow-up, and six subjects (10%) had quit smoking by using another method. However, that study did not have a control group. In a 7-year follow-up of 62 of the original 63 subjects, 28 (45%) had quit smoking, although fewer than half of the subjects ($n=12$) who had quit smoking in that uncontrolled study reportedly had done so by using snuff.[92]

Sweden has been cited as the one example in which moist snuff use apparently replaced smoking for a proportion of men. The pattern of smoking that appears to be emerging in Sweden is a declining but equal prevalence of current smoking for men and women, with a greater proportion of male current smokers than female smokers reporting smoking less than daily (Figure 4). Based on a cross-sectional study of current and former smokers in Sweden,[93] the apparent effectiveness of snuff in helping smokers to quit is modest. Among men, snuff was used at the most recent attempt to quit smoking by 28.7% of former smokers and 23.0% of current smokers ($p=0.072$). Only 4.8% of female current smokers in that study who had attempted to quit and 4.5% of female former smokers ($p=0.85$) reported using snuff during their most recent attempt to quit smoking. Data from one follow-up study conducted in northern Sweden, a region with a high prevalence of moist snuff use (approximately 23% of men and 2% of women), suggest that switching from cigarettes to snuff occurred primarily among men who had prior experience using snuff.[94,95] In that study, complete switching
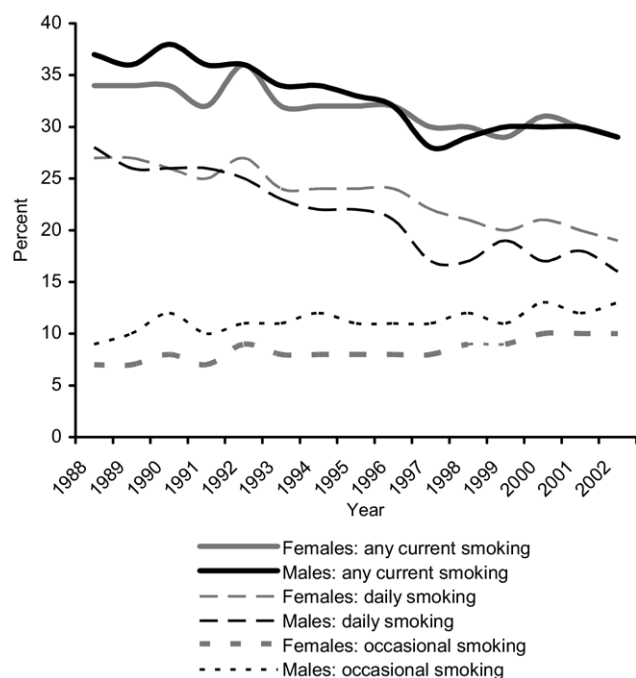

Figure 4. Trends in the proportion of people aged 16–84 years who smoked daily or occasionally, by gender. Sweden, 1988–2002. Data from Statistics Sweden ULF Surveys.

from cigarettes to snuff use was reported by just 8% of men who smoked but had never used snuff at the time of the baseline survey; nearly two thirds of men who smoked had never used moist snuff.

A recent cross-sectional study examined snuff use as a cessation strategy among Swedish adults.[84] Among the 1326 men in that study who were ever-daily smokers, 254 (19%) used snuff as a smoking-cessation aid and 165 (12%) were able to quit smoking completely by using snuff. That accounted for 21% of the 782 male ever-smokers in the survey who had quit smoking completely. Snuff use was a relatively uncommon method of smoking cessation for women; just 66 (5.3%) of the 1249 women who were ever-daily smokers and reported making a smoking quit attempt reported using snuff as their cessation aid. Of the 673 women in this study who had quit smoking completely, 38 (5.7%) reportedly quit by using snuff.

While there is little doubt that snuff has been a useful cessation strategy for some men and women in Sweden, the trend in tobacco use among adults aged 35 years and older does not support a major role for increased snuff use being associated with complete smoking cessation in that country. Figure 5 depicts trends from 1988–1989 through 2004–2005 in the proportion of men and women aged 35–44 years who used snuff daily or were former daily smokers who had stopped completely, based on official Swedish statistics.[86] Among men aged 35–44 years, the prevalence of daily snuff increased from 18.7% to 30.7% during that time period. Women aged 35–44 years also experienced an
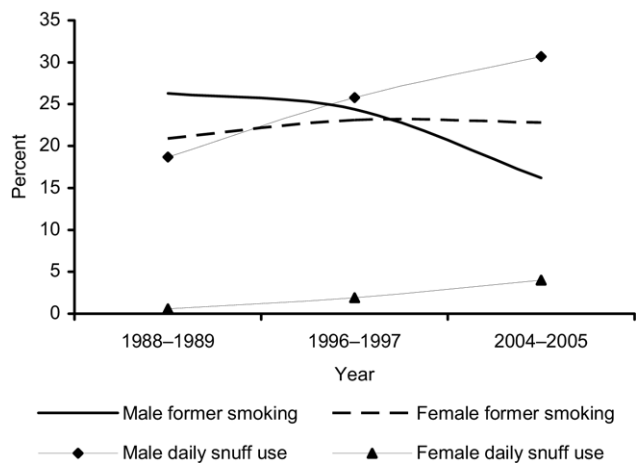
Figure 5. Trends in the proportion of people aged 35–44 years who were former smokers or currently used snuff daily, by gender. Data from Statistics Sweden ULF Surveys.

increased prevalence of daily snuff use between 1988–1989 and 2004–2005, from 0.6% to 4.0%. Although there was an 18–26 percentage point difference between men and women in the prevalence of daily snuff use throughout the time period, the prevalence of former smoking declined for men and increased slightly for women during that time period, despite the prevalence of current smoking being essentially equal for men and women throughout the period.

Tobacco-use patterns men and women aged 35–44 years in Norway are generally consistent with those in Sweden (Figure 6): the prevalence of snuff use by men in that age group increased steeply from 2.9% in 1988 to 16.4% in 2002, but snuff use by women remained rare.[88] Yet, trends in current smoking were essentially identical for men and women aged 35–44 years during that period. While it is difficult to draw firm conclusions from these types of time-series data, the patterns in Sweden and Norway do not suggest that the very large gender differences in the prevalence of snuff use were associated with differences in smoking cessation rates.

There is little information on the proportion of U.S. smokers who have switched completely to the use of smokeless tobacco or have used smokeless tobacco as a method of quitting smoking. Fiore and colleagues[96] reported findings from the 1986 Adult Use of Tobacco Survey on the methods smokers used to quit. That study reported that, in the mid-1980s, 6.8% of former smokers who successfully quit smoking for at least 1 year had substituted other tobacco products (including snuff, chewing tobacco, pipes, or cigars) during any attempt at quitting, and 4.0% of successful quitters substituted other products during their last attempt at quitting. However, the proportions were nearly the same among relapsers: 6.8% of smokers who made a serious quit attempt in the past year but were not successful in

quitting tried substituting other tobacco products in any attempt, and 2.1% tried that strategy during their last attempt at quitting. An earlier report from that survey provided limited information specific to smokeless tobacco use for smoking cessation: 6.4% of current smokers and 7.0% of former smokers used smokeless tobacco to help them quit smoking.[97] More recent data come from the 2000 National Health Interview Survey, in which former smokers were asked what method they had used to quit smoking completely.[98] Just 1% of male former smokers aged 36–47 reported switching to snuff or chewing tobacco to quit smoking. Of male current smokers in that age group who attempted to quit, 0.3% reported switching to smokeless tobacco on their last attempt to quit. In a birth cohort in which 16% of men, including 19% of those who had ever smoked, had used smokeless tobacco by age 34, smokeless tobacco use accounted for a very small proportion of quitting.

In the U.S, the prevalence of smokeless tobacco use varies widely among the states. For example, current use of snuff or chewing tobacco by men aged 15 years or older in 2003 ranged from less than 1% in eight states (HI, NH, DC, MA, RI, MD, CT, and NJ) to more than 10% in three states (WV, MT, and WY) (unpublished data from the 2003 Current Population Survey Tobacco Use Supplement). If smokeless tobacco use were associated with smoking cessation, it might be expected that states with a higher prevalence of snuff use would tend to a have a lower prevalence of current smoking among adult smokers and a higher prevalence of former smoking. However, the prevalence of daily snuff use among men aged 25–44 was significantly positively associated with the prevalence of daily smoking among the 50 U.S. states and the District of
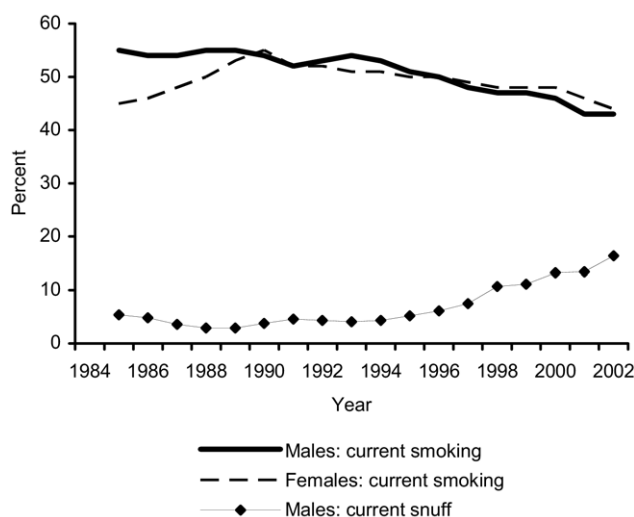

Figure 6. Trends in the proportion of people aged 35–44 years who currently used snuff (daily or occasionally) or currently smoked (daily or occasionally), by gender. Norway, 1985–2002. Data from Statistics Norway.
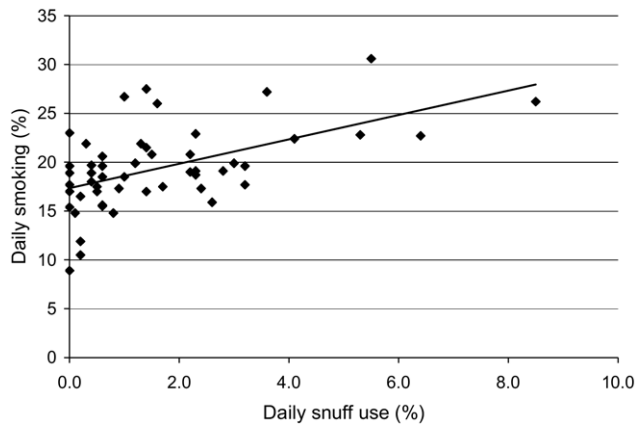
Figure 7. Scatter plot and fitted linear regression line for prevalence of daily smoking and daily snuff use among men in the 50 states and the District of Columbia. United States, 2003. Data from the 2003 Current Population Survey Tobacco Use Supplement.

Columbia (r=0.54, p<0.0001; Figure 7) and significantly negatively associated with the prevalence of former smoking (r=−0.27, p=0.06; Figure 8).

Smokeless Tobacco and Cigarette Consumption

The third potential mechanism by which smokeless tobacco theoretically could reduce tobacco harm is by serving as a partial substitute for cigarettes among continuing smokers. There is some evidence that "dual users" of cigarettes and smokeless tobacco smoke fewer cigarettes, on average, than do exclusive smokers. An analysis of data from the 2000 National Household Survey on Drug Abuse found that dual users smoked on fewer of the preceding 30 days than did exclusive smokers (19.86±12.16 vs 23.14±10.92; p<0.0001) and smoked fewer cigarettes per day on the days they smoked (3.73±1.59 vs 4.01±1.52; p<0.0001).[99]

Analysis of data from the 2000 National Health Interview Survey (NHIS) found that smokers who also used snuff every day smoked, on average, fewer cigarettes per day than did exclusive smokers (11.4 vs 18.4; p=0.0001).[100] However, smokers who used snuff only on some days did not differ from those who never used snuff in the mean number of cigarettes smoked per day (19.3 vs 18.4; p=0.42). Occasional snuff users consisted of 44% of all current snuff users, compared to 18% of current smokers who did not smoke every day. The prevalence of daily smoking was lower among daily snuff users (11.7%; 95% CI=±4.2%) than among men who never used snuff (20.9%; 95% CI=± 0.9%). However, the prevalence of daily smoking (32.7%; 95% CI=±7.5%) and occasional smoking (6.2%; 95% CI=±3.2%) was fairly high among occasional snuff users. Dual users of cigarettes and snuff accounted for about one third of all current snuff users. Detailed histories of initiation and reasons for dual use cannot

be determined from these types of cross-sectional studies, but the patterns are consistent with a substantial proportion of the snuff consumed in the United States being used by current smokers as a complementary source of nicotine. Recent data suggest that more than one in four adult male smokers in ten U.S. states use another form of tobacco in addition to cigarettes.[101]

Responses to Smokeless Tobacco Marketing
United States

Smokeless tobacco products, predominantly chewing tobacco, commanded a large share of the tobacco market in the U.S. in the early 20th century, but began a decline in popularity in the 1920s. Smokeless tobacco products were heading toward extinction by 1970, when chewing tobacco or snuff use was largely limited to people aged 65 years and older.[102] A sharp increase in the use of smokeless tobacco in the U.S., especially use of moist snuff, began in the early 1970s. That increase was the result of the development of new products designed to appeal to novice users, a "graduation" marketing strategy intended to promote nicotine addiction, and heavy promotion by U.S. Tobacco Company (now called the U.S. Smokeless Tobacco Company), the major U.S. manufacturer of moist snuff.[103,104] The greatest increase in the use of moist snuff occurred among young men. For example, the prevalence of moist snuff by men aged 18–24 years increased ninefold between 1970 and 1987, from 0.7% to 6.4%, while it declined among men aged 45 years and older during that time period.[102]

Sweden

Sweden experienced a pattern similar to the U.S. in response to aggressive marketing by the Swedish Match
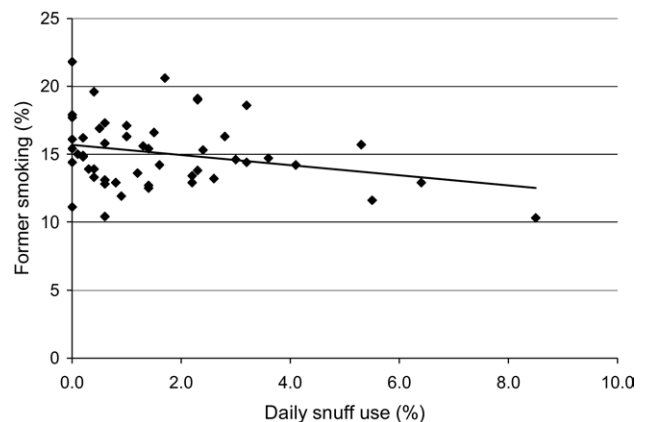

Figure 8. Scatter plot and fitted linear regression line for prevalence of former smoking and daily snuff use among men aged 25–44 years in the 50 states and the District of Columbia. United States, 2003. Data from the 2003 Current Population Survey Tobacco Use Supplement.

Company, that country's primary manufacturer of smokeless tobacco products. By the late 1960s, less than 10% of boys and young men used snuff and the typical user was an older, rural male laborer.[105] Starting in the late 1960s, Swedish Match Company increased the attractiveness of its products' packaging, introduced new brands, and began an aggressive advertising campaign. As a result, moist snuff consumption, which had been declining for nearly 5 decades, began a sharp increase. Within 4 years, the prevalence of snuff use doubled among men aged 15–19 years, from 11% in 1969–1970 to 22% in 1972–1973. The prevalence of snuff use among men aged 30 years or older remained virtually unchanged during that time period. The median age of snuff users in Sweden declined from 41 years in 1969–1970 to 30 years in 1972–1973.

Conclusion

The available data suggest that there is weak and inconsistent evidence for smokeless tobacco promotion as a public health strategy for harm reduction. When aggressively promoted in industrialized countries, history suggests that initiation of moist snuff use occurs almost entirely among adolescent and young adult men. Although some proponents claim that uptake of snuff may prevent the initiation of smoking, the available evidence does not support that claim. To the contrary, prospective cohort studies of young people in the U.S. suggest that smokeless tobacco use is predictive of subsequent smoking. Trends in tobacco prevalence in the U.S. and Norway do not support the contention that the growth in moist snuff was associated with a reduction in smoking initiation. Trends in Sweden suggest that snuff provided a partial substitution for cigarettes mostly among men, but the prevalence of smoking in that country is essentially equal for men and women. Some adult smokers in Sweden clearly used snuff as a method for quitting smoking, but snuff use explains, at best, a relatively small proportion of the decline in smoking. The prevalence of smoking remains relatively high among snuff users in all three countries considered in this review. There are no data on the efficacy of snuff as a smoking cessation method.

Moist snuff products are addictive, carcinogenic, and destructive to periodontal tissues, and appear to increase the risk for adverse birth outcomes and possibly cardiovascular diseases. The abuse potential for these products is high. There are nearly no published cohort studies on risk reduction among smokers who switch to using moist snuff. In Sweden, the role of snuff in reducing smoking is unclear but almost certainly overstated. Those who embrace the "Swedish experience" as a model for tobacco harm reduction[73,106–108] do not address the U.S. and Norwegian experiences with moist snuff, in which their growth in popularity simply added to the burden of tobacco use. Interestingly, 44 of the 50

states in the United States have achieved a prevalence of smoking equal to or lower than Sweden's, with very little use of smokeless tobacco in most states.[109] Five of the six states with a higher prevalence of smoking than Sweden have among the highest prevalence of smokeless tobacco use in the United States. Some proponents for smokeless tobacco as a harm reduction strategy for smoking advocate differential taxation on tobacco products based on their risk and communications from the public health community that conveys the varying levels of risk.[6,110] These are directions that require future investigation. However, there presently remains little evidence that marketing or promotion of smokeless tobacco products as alternatives to cigarettes is an effective strategy for reducing smoking or societal harm from tobacco use.

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Genetics and Smoking Cessation
Improving Outcomes in Smokers at Risk

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Abstract: This article reviews evidence supporting the potential utility of a pharmacogenetic approach to the treatment of nicotine dependence. There is substantial evidence that nicotine dependence and smoking persistence are heritable, and are determined by a complex interplay of polygenic and environmental influences. The most robust evidence for specific genetic influences on nicotine dependence is found in studies of genetic variation in nicotine-metabolizing enzymes. Data also support the role of genes in the dopamine and opioid pathways as predictors of dependence and smoking relapse; however, the evidence for genetic associations is not always consistent. Emerging data from pharmacogenetic trials of nicotine-dependence treatment are promising, suggesting that genetic profiles of smokers someday may be used by providers to choose the type, dose, and duration of treatment for individual smokers. However, additional trials including larger and more diverse populations are needed before such data can be translated to practice to reduce smoking prevalence and tobacco-related disease.
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Introduction

Despite progress made in the treatment of tobacco dependence, currently available treatments are effective for only a fraction of smokers. Although current guidelines recommend the use of nicotine patch as a firstline treatment for tobacco dependence,[1] about 70%–80% of smokers treated with the patch relapse to their former smoking practices in the long-term.[2,3] Bupropion has been shown to produce higher quit rates than nicotine replacement therapy,[4,5] yet the large majority of smokers do not quit nor do they remain abstinent. The newly FDA-approved medication for treating nicotine dependence, varenicline, which outperforms bupropion significantly, yields a 1-year abstinence rate of 22%. However, these quit rates were achieved with behavioral counseling lasting for almost 1 year, which may not reflect real-world treatment.[6,7] Thus, research is needed to identify those smokers who are at increased risk for relapse following a cessation attempt, and to tailor smoking-cessation treatments to smokers' individual risks and needs.

Pharmacogenetics research is generating new knowledge about genetic factors that influence nicotine dependence and smoking-cessation treatment outcomes. The basic premise of this approach is that inherited differences in drug metabolism (pharmacokinetics) and drug targets (pharmacodynamics) have important effects on treatment outcome.[8,9] These concepts and key variables are illustrated for nicotine-dependence treatment in Figure 1. Efforts to increase the understanding of the role that inherited variation plays in response to pharmacotherapy for nicotine dependence someday may help practitioners to individualize treatment type, dose, and duration based on genotype, thereby minimizing adverse reactions, increasing treatment compliance, and maximizing treatment efficacy.[10,11] This article reviews evidence supporting the potential utility of a pharmacogenetic approach to smoking-cessation treatment. Portions of this paper were adapted from a recent book chapter on this topic.[12]

Genetic Influences on Smoking Persistence and Relapse

While the initiation of tobacco use, the progression from use to nicotine dependence, and the ability to quit smoking are influenced by a range of environmental factors (e.g., parental and peer influence, depression), twin studies have shown that genes play a critical role as well.[13,14] In twin studies, evidence of heritability is based on evaluating the similarity between monozygotic twins (who share 100% of their genes) on a phenotype, compared to dizygotic twins (who share 50% of their genes, similar to nontwin siblings). These studies have shown that approximately 60%–70% of the variability in nicotine dependence and smoking persis-

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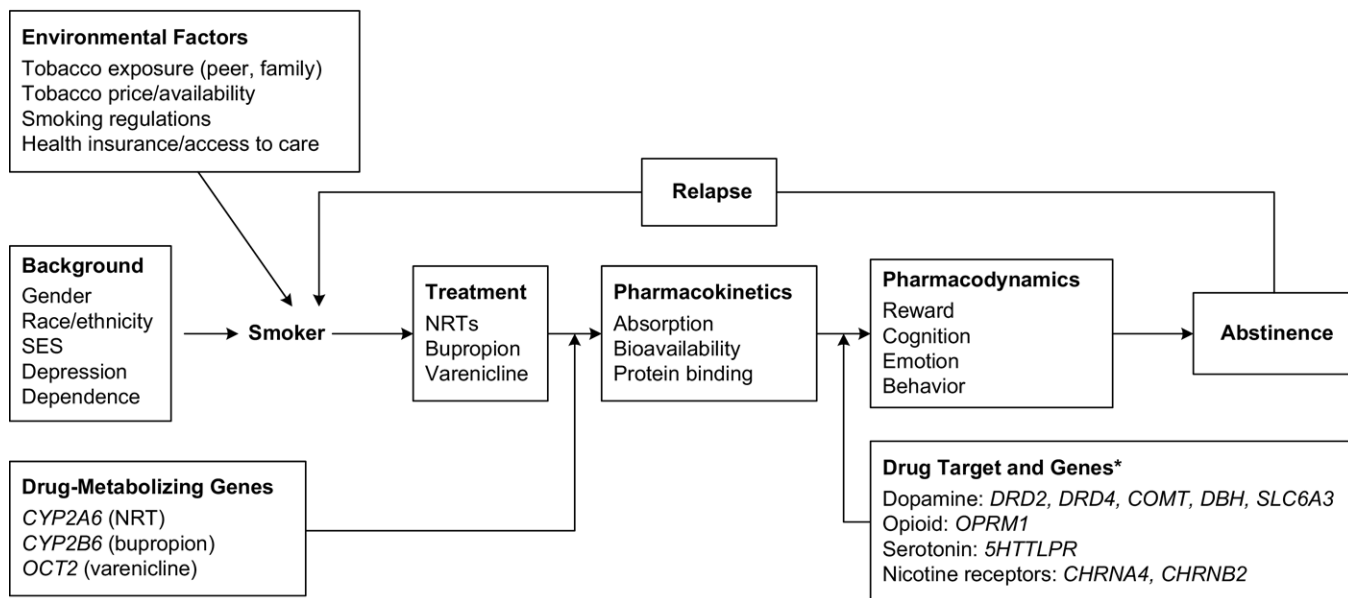
Figure 1. A pharmacogenetic model of nicotine-dependence treatment. * indicates that genes shown include the subset examined for pharmacogenetic effects.
nAChRs, nicotinic acetylcholine receptors; NRT, nicotine replacement therapy; SES, socioeconomic status.

tence is due to genetic influences.[13,15–21] Two recent studies examined smoking-cessation data from twin pairs from the Vietnam Twin Registry[22,23] and concluded that 51%–54% of the variance in the ability to quit smoking given a quit attempt, was attributable to genetic factors.

Given consistent evidence for the heritability of nicotine dependence, attention has shifted to investigations of specific genetic influences.[24–26] Genetic variation in enzymes (e.g., CYP2A6) that metabolize nicotine to its inactive forms (cotinine and 3-hydroxycotinine) influence peripheral levels of nicotine and smoking behaviors.[25] Genetically faster metabolizers of nicotine (two *1 alleles; ~80% of smokers)[27] smoke more cigarettes per day and are more dependent on nicotine than slower metabolizers (carriers of *2 *4, *9A, and *12A alleles; ~20% of smokers)[27,28] Fast metabolizers are also two times less likely to quit smoking,[29] are more likely to relapse following transdermal nicotine-replacement treatment,[30] and report higher levels of withdrawal symptoms following cessation.[31]

Candidate genes in neurobiological pathways mediating drug reward have been extensively studied for associations with nicotine dependence. Nicotine binds to neuronal nicotinic acetycholine receptors (nAChRs) expressed on dopamine and gamma-aminobutyric acid (GABA) neurons in the ventral tegmental area (VTA), resulting in increased dopamine release in the nucleus accumbens.[32,33] Despite the importance of nAChRs in nicotine dependence, particularly the CHRNA4 and CHRNB2 subtypes,[34] functional polymorphisms in these subunit genes have yet to be identified. Selected genetic polymorphism and haplotypes in CHRNA4 have

been associated with nicotine dependence,[35,36] while studies examining the role of CHRNB2 in smoking behavior have been negative.[35,37,38]

Given the central role of dopamine signaling in the rewarding effects of nicotine, alcohol, and other addictive drugs,[39–41] many initial studies focused on the common Taq1A polymorphism, originally thought to be in the dopamine D2 receptor (DRD2) gene, but later determined to be in a neighboring gene, ANKK1.[42] With respect to smoking behavior, some association studies have reported a higher prevalence of the low-activity DRD2 Taq1'A1 allele among smokers compared to nonsmokers,[43,44] while other findings have been negative.[45] Positive results have also been reported for associations of a variable number tandem repeat (VNTR) polymorphism in the 3″ end of the dopamine transporter (SLC6A3) gene with smoking behavior[46,47]; however, this has not been replicated in other studies.[48] Finally, two independent studies have provided evidence for interacting effects of the DRD2 Taq1A and SLC6A3 variants on the likelihood of cessation.[49,50] A separate study found associations of SLC6A3 genotypes with cessation following treatment with either nicotine replacement therapy (NRT) or bupropion.[51]

More robust findings have been observed for polymorphisms shown to alter protein transcription or translation. For example, the reduced-activity 7-repeat allele of the DRD4 gene VNTR has been associated with smoking persistence in African Americans.[52] The high-activity (Val) allele of the catechol-o-methyl-transferase (COMT) gene, associated with more rapid degradation of dopamine, has been associated with smoking persis-

tence in a retrospective case-control study and in a prospective smoking-cessation study.[53]

Nicotine also increases levels of endogeneous opioids that bind to mu opioid receptors on GABA interneurons in the VTA.[41] Consistent with neurobiological evidence, the mu opioid receptor (*OPRM1*) Asn40Asp functional variant (low-activity Asp40 allele) has been associated with smoking persistence,[54] as well as reduced nicotine reward among women.[55] A recent study comparing smokers with high vs low levels of nicotine dependence did not find associations with this *OPRM1* variant; however, haplotype analysis suggests that other variants, that may be in linkage disequilibrium with the Asn40Asp polymorphism, are linked with this smoking phenotype.[56] Finally, despite effects of nicotine on serotonin neurotransmission, there is no strong evidence linking smoking cessation with genes in the serotonin pathway,[57–59] although associations with nicotine dependence have been reported.[60] Thus, it has proven difficult to identify candidate genes with robust, replicable associations with nicotine dependence and smoking persistence.

Pharmacogenetic Investigations of Treatment for Nicotine Dependence

Pharmacogenetic clinical trials, in which the type and dose of treatment are under experimental control, may provide a stronger signal for genetic effects on smoking cessation and shed light on individual differences in the efficacy of treatments for nicotine dependence (see Table 1).[61] The emerging field of pharmacogenetics is based on the premise that inherited genetic variants contribute to individual variability in treatment toxicity and efficacy.[8,9] Although this field is in its formative years, identifying genes related to responsiveness to treatments for nicotine addiction can lead to clinical guidelines for tailoring treatments to genetic profiles to increase treatment efficacy.[10,61]

Nicotine Replacement Therapy Trials

To date, two pharmacogenetic trials of NRT have been conducted. The first of these, conducted in the United Kingdom, compared transdermal nicotine patch to placebo patch among 755 of 1500 smokers who consented to provide DNA following the initial efficacy trial.[62,63] Based on previous evidence that nicotine's rewarding effects are mediated, in part, by dopaminergic mechanisms,[64,65] initial pharmacogenetic analyses focused on genes in the dopamine reward pathway. The patch was found to be superior to placebo for carriers of the Taq1 A1 allele of the *DRD2* (ANKK1) gene, but not those homozygous for the more common A2 allele.[62] Further, the short-term efficacy of the transdermal nicotine patch was modulated by synonymous single-nucleotide polymorphism (SNP) in the

dopamine beta hydroxylase (*DBH*) gene, which codes for an enzyme involved in the conversion of dopamine to norepinephrine.[63] A longer-term follow-up of this analysis supported the association of the *DRD2* Taq1A variant with abstinence at 6- and 12-month follow-ups; however, the effect was observed only among women.[62] These findings suggest that the efficacy of pharmacotherapy may be influenced by different genetic and biological factors in men and women.

In the United States, an open-label randomized trial compared transdermal nicotine and nicotine nasal spray. A recent pharmacogenetic analysis from this trial focused on two functional genetic variants in *DRD2*.[66] A promoter variant (–141C Ins/Del) is associated with altered transcriptional efficiency.[67] Another functional SNP in *DRD2* (C957T) alters mRNA stability and protein synthesis.[68] Smokers carrying the reduced activity *Del* C allele of the –141C had statistically significantly higher quit rates on NRT compared to those homozygous for the *Ins* C allele, independent of NRT type. The C957T variant also was associated with abstinence following NRT. Thus, smokers carrying variants associated with reduced transcriptional efficiency or translation responded better to NRT, perhaps because of nicotine's effects on dopamine release. Separate analyses from this trial reported that success with NRT was predicted by an interaction between the *DRD2* –141 *Ins/Del* SNP and the NCS-1 gene, coding for a *DRD2* interacting protein.[69]

The role of the *COMT* Val/Met functional polymorphism was also explored for effects on response to NRT in this trial.[53] COMT is the primary enzyme involved in the degradation and inactivation of the neurotransmitter dopamine. A polymorphism in *COMT* results in conversion of a Val high-activity allele to a Met low-activity allele, resulting in a three- to four-fold reduction in *COMT* activity. In the NRT trial, the Met/Met genotype was associated with a higher probability of abstinence with either nicotine nasal spray or nicotine patch, among women, but not in men.[53]

The role of the *OPRM1* gene was also examined in the U.S. trial.[54] The Asp40 variant (G allele) is associated with reduced MRNA and protein levels[70] and is carried by 25%–30% of individuals of European ancestry. In the NRT trial, smokers carrying the *OPRM1* Asp40 variant were significantly more likely than those homozygous for the Asn40 variant to be abstinent at the end of the treatment phase. The differential treatment response was most pronounced among smokers receiving transdermal nicotine.[54] In contrast to positive associations for *DRD2* and *OPRM1*, there was no evidence for moderation of treatment response by the serotonin transporter (*5-HTTLPR*) gene in the NRT trial.[58] Likewise, David et al.[57] reported that response to NRT was not associated with variants of the *5-HTTLPR* gene.

Finally, a recent paper reported the effects of SNPs in *CHRNA4* (α4 subunit of the acetycholine nicotinic

Table 1. Summary of pharmacogenetic effects in nicotine-dependence clinical trials

Genes	Treatment	Gender interaction	Main finding	Citation
Pharmacokinetics/drug metabolizing enzymes				
CYP2A6	NRT	Not reported	Genotypes related to 3-HC/cotine ratio; slow metabolizers smoke fewer cigarettes and are less nicotine dependent; in patch condition, slow metabolizers had higher plasma nicotine but equal patch use; in spray condition, fast metabolizers used more spray but had equal plasma nicotine	28
CYP2A6 (3-HC/ Cotinine Ratio)	NRT	Not reported	3-HC/cotinine ratio predicted nicotine patch efficacy but not nasal spray; there was a 30% reduction in chance of cessation following patch therapy with each increasing quartile of metabolite ratio	30
CYP2B6	Bupropion	Yes	Slow metabolizers had increased cravings after quitting and higher relapse rates; bupropion attenuated theses effects among females	74
	Bupropion	No	Among smokers with decreased bupropion metabolism, bupropion produced significantly higher abstinence rates than placebo; bupropion was no more effective than placebo for smokers with normal bupropion metabolism	75
Pharmacodynamics/drug target genes				
DRD2 (Taq 1A)	NRT	Yes	Quit rates from patch therapy were higher for women with the Taq1 A1 allele, but there was no genotype effect for men	62
	NRT	No	Quit rates from patch therapy were significantly greater for smokers with the Taq1 A1 allele and the *DBH* A allele	63
	Bupropion	Yes	Women with the *DRD2* A2/A2 allele were more likely to quit smoking, compared to women with A1 alleles	80
	Bupropion	No	Those with *DRD2* A2/A2 alleles showed better treatment response, versus those with A1/A1 or A1/A2 alleles	78
	Venlafaxine		Smokers with the *DRD2* A1 allele (A1/A1/A2) quit significantly less often than the homozygous A2s	79
DRD2 (−141 *Ins/Del*)	NRT	No	Smokers homozygous for the *Del* C allele responded better to NRT than carriers of the *Ins* C allele	66
	Bupropion	No	Smokers homozygous for the *Ins* C allele had higher quit rates following bupropion, versus smokers with the *Del* C allele; smokers with the *Del* C allele had higher quit rates on placebo	66
	NRT	No	Smokers with at least one copy of the −141 *Del* allele and two copies of the *FREQ* rs1054879 A allele were more likely to quit smoking , compared to smokers with other alleles	69
DRD2 (C957T)	NRT	No	Smokers with CT/CC genotypes were less than two-thirds as likely to be abstinent, versus participants with TT genotypes	66
	Bupropion	No	Variants of C957T were not associated with quit rates following bupropion therapy	66
DBH	NRT	No	Smokers with the *DBH* GA/AA genotype had higher quit rates, compared to those with GG alleles	63
COMT	NRT	Yes	Women with the Met/Met genotype showed higher quit rates following NRT, versus women with the Val/Val allele	53
	Bupropion	No	COMT haplotype from SNPs rs165599 and rs373865 affected response to bupropion, with higher quit rates among smokers carrying the A allele of the rs165599 (A/G) SNP	82
SLC6A3	Bupropion	No	Smokers with *DRD2-A2* genotypes and *SLC6A3-9* genotypes, versus *SLC6A3-10* genotypes, had significantly higher quit rates and a longer latency to relapse	50
	NRT or bupropion	No	Smokers with the 9-repeat allele were more likely to quit smoking following treatment than those with 10/10 repeats	51
	Bupropion	No	There were no main effects for *DRD2* and *SLC6A3* genotypes on smoking cessation; those with DRD2 A1 and *SLC6A3* 9-repeat alleles show poorer response to bupropion	49
OPRM1	NRT	Yes	Quit rates following treatment were higher for carriers of the OPRM1 Asp40 variant, versus carriers of the Asn40	54
5-HTTLPR	NRT	No	*5-HTTLPR* alleles were not related to NRT response	58
	NRT	No	*5-HTTLPR* alleles were not related to NRT response	57
CHRNA4	NRT	No	Smokers with the TC genotype were more likely to maintain abstinence on nasal spray, but not transdermal patch	71

3-HC, 3-hydroxycotinin; NRT, nicotine replacement therapy.

receptor) in response to NRT in the U.S. clinical trial.[71] Individuals with the TC genotype for this SNP, which is associated with greater $\alpha4\beta2$ binding and greater sensitivity to the acute effects of smoking, were more likely to maintain abstinence on nasal spray, but not transdermal patch.

Bupropion Trials

To date, three independent bupropion pharmacogenetic trials have been conducted in the U.S. An initial report from a placebo-controlled trial focused on the *CYP2B6* gene, which has been implicated in bupropion kinetics[72] as well as in brain metabolism of nicotine.[73] Participants in this trial provided blood samples and received bupropion (300 mg/day for 10 weeks) or placebo, plus counseling. Smokers with a decreased-activity variant of *CYP2B6* (slower metabolizers) reported greater increases in cravings for cigarettes following the target quit date and had significantly higher relapse rates.[74] These effects were modified by a significant gender X genotype X treatment interaction, suggesting that bupropion attenuated the effects of genotype among female smokers. The absence of a genotype association with bupropion side effects suggests that the genotype effect is not due to bupropion pharmacokinetics, but may be attributable to *CYP2B6*-mediated differences in nicotine metabolism in the central nervous system (CNS). For example, slower metabolizers of CNS-nicotine may experience neuroadaptive changes that promote dependence and abstinence-induced craving. In a subsequent analysis of a novel functional *CYP2B6* *6 variant (a genotype combining 2 SNPs), smokers with this genotype had significantly lower quit rates on placebo, and responded very well to bupropion; in contrast, smokers with the wildtype genotype performed equally well on placebo and bupropion.[75]

Inhibition of dopamine reuptake is one putative mechanism for the beneficial effects of bupropion.[76,77] Therefore, an analysis of response to bupropion has been conducted relative to two functional genetic variants in *DRD2*. There was a statistically significant interaction between the *DRD2* –141C *Ins/Del* genotype and treatment, at the end of the treatment phase, indicating a more favorable response to bupropion among smokers homozygous for the *Ins* C allele compared to those carrying a *Del* C allele.[66] The C957T variant was not associated with bupropion response. Given that the –141 *Ins* C allele results in higher transcriptional efficiency compared to the *Del* (N) allele,[67] individuals with the –141C *Ins/Del* CC genotype may have more D2 receptors available to bind dopamine, yielding a more rewarding experience of the nicotine-induced dopamine release. Blockade of dopamine reuptake by bupropion may be more effective in promoting absti-

nence in the *Ins C* genotype group due to greater ability to bind dopamine.

David et al.[78] examined the *DRD2*, the dopamine transporter gene *SLC6A3*, and the *CYP2B6* (C1459T) genotypes as moderators of treatment response in a placebo-controlled bupropion trial with 283 smokers of European ancestry. Smokers with the *DRD2* Taq1-A2/A2 genotype had a significantly better treatment response (35% for bupropion and 12% for placebo), compared to smokers with A1/A1 or A1/A2 genotypes (21% for bupropion and 24% for placebo). Cinciripini and colleagues[79] examined the *DRD2* Taq1A polymorphism in a placebo-controlled trial of venlafaxine (a serotonin reuptake inhibitor) and reported that smokers carrying the A1 allele were less likely to quit.

Swan and colleagues[80] examined the role of the *DRD2* Taq1A polymorphism in an open-label, randomized effectiveness trial comparing 150 mg and 300 mg doses of bupropion. Compared to women homozygous for the A2 allele, women with at least one A1 allele were significantly less likely to quit smoking and more likely to report having stopped taking bupropion due to treatment side effects. Finally, a recent analysis from the bupropion placebo-controlled trial provides preliminary evidence for associations of a *COMT* haplotype with bupropion response.[81]

Summary, Clinical Implications, and Future Research Directions

Initial findings presented in this review support the role of genetic variation in response to bupropion and NRT for smoking cessation (see Table 1). Variations in genes in the dopamine and opioid pathways, and in nicotine-metabolizing enzymes, appear to play a role in the efficacy of nicotine-replacement therapy, while genetic variation in the dopamine pathway also appears to be important for response to bupropion. Many of these studies also provide evidence for gender heterogeneity in these genetic associations.

While the integration of genetic testing into standard clinical practice would be premature at this time, pharmacogenetic studies of treatments for nicotine dependence eventually may guide individualized smoking-cessation treatments. For instance, carriers of genetic variants that increase nicotine metabolism may not respond as well to standard NRT doses, whereas carriers of reduced-activity variants in *DRD2* (e.g., Taq 1A, –141 DelC) may respond particularly well to NRTs. Selecting smokers with reduced-activity *DRD2* variants for NRT or selecting smokers with genetic variants that increase nicotine metabolism for a higher dose of NRT may enhance long-term quit rates. Importantly, many of the genetic variants linked to nicotine dependence and poor response to treatments are very common, such as *CYP2A6*1* (77%)[27] and *DRD2* A1 (43%),[50]

suggesting that genetically-tailored treatment approaches could have a substantial population-level impact on treatment outcomes. In addition, the effect size associated with the presence of genetic alleles linked to smoking phenotypes is typically meaningful. For instance, 35% of smokers homozygous for the *Ins* C allele were abstinent following bupropion treatment, compared to only 20% of smokers carrying a *Del* C allele.[66] Likewise, at the end of NRT treatment, 23% of carriers of the Taq1 A1 allele of the *DRD2* (*ANKK1*) gene were abstinent, compared to 13% of those homozygous for the more common A2 allele.[62] Further, pharmacogenetic studies also may help researchers understand the neurobiology of nicotine dependence which, in turn, could guide the development of new treatments. Thus, given the frequency and impact of genetic alleles linked to smoking phenotypes, using genetic information to tailor the selection of treatments may ultimately have a substantial impact on overall rates of smoking.

The use of genetic information to tailor the selection of treatments for nicotine dependence is feasible, yet there are several important policy issues that must be addressed before this technology will become standard clinical practice. First, while genetic testing for smoking genotypes increasingly is becoming more affordable and efficient with advances in technology, testing largely remains confined to the context of research programs. Decisions about how the costs of testing will be covered and whether or not insurance companies will absorb these costs have yet to be bridged. Further, given the limited resources of middle- or low-income countries, it appears likely that the potential benefits of using genetic information to treat nicotine dependence would only be realized in high-income countries. Even with adequate resources in high-income countries to implement genetic testing into treatment for nicotine dependence, researchers will need to demonstrate that such a treatment approach is cost-effective. To date, cost-effectiveness analysis of genetic testing for nicotine-dependence treatment has only recently begun,[82] and remains as a critical priority for future research.

Further, as genetic testing for nicotine dependence is incorporated into clinical practice, researchers and clinicians must be mindful of the role of race/ethnicity as factors that influence smoking phenotypes and genes related to nicotine dependence. To date, the vast majority of studies have been conducted with Caucasians to avoid population stratification bias. Race/ethnicity influence smoking behavior (e.g., age of initiation, smoking rate, level of dependence)[83] and there are large racial differences in allele frequencies for nicotine-metabolizing genes[25,84] and dopaminergic genes.[85] Further, since access to healthcare and socioeconomic status vary with race/ethnicity, the potential implementation of genetic testing clinical services may need to consider race/ethnicity as an important variable if the potential for this technology is to be realized.[84,86]

Third, there is substantial comorbidity between nicotine dependence and other substance abuse conditions and psychiatric disorders, including depression, schizophrenia, attention-deficit hyperactivity disorder, anxiety, and personality disorders.[33] In addition, genes linked to smoking behavior and treatment response may be related to psychiatric conditions and other addictions.[87] Thus, genetic testing to tailor treatment for nicotine dependence simultaneously could identify individuals with other dependence or psychiatric disorders,[88] and treatment programs may need to be prepared to provide more comprehensive interventions to ensure efficacy and to address comorbid psychiatric conditions.

Fourth, several genes and environmental factors likely combine to influence response to treatments for nicotine dependence. To date, most studies have focused on single genes and have not evaluated gene–environment interaction. The development of effective individualized treatments for nicotine dependence and moving beyond a "one size fits all" model may depend on future pharmacogenetic studies that include sufficiently large samples to evaluate gene–gene and gene–environment interactions.

Finally, if genetic testing for nicotine dependence is to be incorporated into clinical practice, primary care physicians, who are often the first point of contact for patients seeking assistance with quitting, will need to be appropriately trained. Many physicians lack confidence to provide genetic testing,[89] underscoring the need for guidelines to help physicians integrate genetic testing into their practice.

Additional work is needed to validate these findings across independent trials. Meta-analytic techniques also may be applied to overcome issues related to the relatively small sample sizes of the initial trials.[90] Future studies also should explore the use of more refined outcome measures that account for the longitudinal trajectories of smoking cessation, including multiple lapses, relapses, and changes in smoking rates over time.[91] Increased attention to gender heterogeneity in genetic associations[55] as well as ethnic heterogeneity is needed. In addition, future studies should also explore the influence of genetic variation in additional genetic pathways relevant to nicotine dependence, including GABA and glutamate. Such studies may hold great promise for the identification of novel biological targets for drug development and improvement in the delivery of nicotine-dependence treatment to reduce the morbidity and mortality caused by smoking.

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Nicotine Interventions with Comorbid Populations

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Abstract: This article reviews and comments on studies of treatment and prevention of cigarette smoking in individuals with comorbid psychiatric and non-nicotine substance abuse disorders. Despite a high prevalence of cigarette smoking in these populations and interest in quitting, treatment interventions and studies of these interventions are sparse. Multiple barriers to implementation of interventions exist. Existing data suggest that provision of cigarette-smoking interventions in substance abuse treatment patients is efficacious and does not appear to interfere with abstinence from alcohol or illicit drugs, but more research is needed. There are few studies in populations with psychiatric disorders, with the exception of studies of individuals with a history of major depressive disorder. The available data suggest at least moderate efficacy and little evidence of exacerbation of these disorders. Integration of interventions into existing treatment clinics appears desirable. Despite the identification of subgroups that are especially likely to adopt cigarette smoking, there have been no targeted prevention efforts. Further research is recommended in both the treatment and prevention of cigarette smoking in individuals with psychiatric and substance abuse disorders. It is reasonable to offer existing treatments to these subgroups of smokers, since there is some evidence of efficacy and little evidence of harm.
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Introduction

The goal of this article, which was first presented as a conference paper at a State of the Science Conference in August 2006, was to selectively review the studies on smoking treatment for individuals with psychiatric or non-nicotine substance abuse disorders. The article outlines five areas felt to be of importance: (1) prevalence of smoking in individuals with psychiatric and substance abuse disorders; (2) readiness for change in comorbid smokers; (3) outcome data on the treatment of cigarette smoking in comorbid individuals; (4) the effect of smoking cessation and smoking treatment on the recurrence of the non-nicotine substance abuse disorders, or on the symptoms of the psychiatric disorder; and (5) prevention, or more accurately, the lack of studies in prevention, and potential areas where prevention efforts and studies might be directed.

This is not a comprehensive review of the studies on smoking cessation in comorbid individuals. Rather, studies were selected that illustrate major issues in the research on the treatment of comorbid smokers. Some studies, especially large-scale clinical trials, studies with particularly important findings, and a meta-analysis, are described in some detail since these studies bring a richness of data and findings to the area. The paper does not attempt to address the complex etiologic issues relevant to comorbidity in each of these disorders, nor does it present theories that link smoking and mental disorders and non-nicotine substance abuse disorders. Comorbidity in each disorder is linked with different and, in the case of depression and schizophrenia, multiple, etiologic and theoretic models. A discussion of these complex models is beyond the scope of this paper.

Individuals who are dually diagnosed with psychiatric and non-nicotine substance abuse disorders are disproportionately affected by tobacco dependence. Individuals previously treated for alcoholism and/or other non-nicotine drug dependence have an increased cumulative mortality due more to tobacco-related than to alcohol-related causes.[1] A population study using data from the National Comorbidity Survey estimates that 41.0% of the individuals with current major mental disorders smoke cigarettes, and 44.3% of the cigarettes consumed in the United States are smoked by individuals with a mental illness.[2] In this study, the highest rates of smoking prevalence were among those with bipolar disorder, generalized anxiety disorder, and drug and alcohol dependence. Furthermore, using data from the National Epidemiologic Survey on Alcohol and Related Conditions, Grant et al.[3] found high nicotine-dependence prevalence rates in individuals with drug and alcohol disorders, and in individuals with any of seven personality disorders (avoidant, dependent, obsessive–compulsive, paranoid, schizoid, histrionic, and antisocial).[3]

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Disproportionate prevalence of smoking also occurs in individuals in treatment for psychiatric and substance abuse disorders. Rates vary among individuals engaged in mental health treatment depending on disorder and treatment modality (i.e., inpatient or outpatient), but are consistently higher than the general population.[4–7] Multiple studies show high rates of smoking among drug-treatment patients, ranging from 74% to 88%.[8,9]

Reasons for Quitting Smoking Unique to Comorbid Smokers

Individuals with comorbid disorders have the same incentives to quit smoking as any smoker, including longer life, better quality of life, and the health of those exposed to environmental tobacco smoke. There are additional reasons to encourage abstinence among smokers with comorbid disorders. For example, studies demonstrate that individuals with non-nicotine substance abuse disorders and nicotine dependence may be more likely to abstain from the other problem substance if they quit smoking.[10] Further, the health impact of smoking in comorbid populations is severe. For example, Hurt et al.[1] found that smokers with alcohol problems were more likely to die of a smoking-related illness than one related to alcohol. Cigarette smoking may interact with other drugs, complicating recovery from psychiatric disorders. Cigarette smoking accelerates the metabolism of many drugs used to treat psychiatric disorders,[11] making higher levels of medication necessary and introducing the possibility of fluctuating medical blood levels as a function of changes in smoking. In a similar vein, a cross-sectional study comparing alcohol-dependent smokers and non-alcohol-dependent smokers suggests that nicotine may augment the reinforcing effects of alcohol, thus making abstinence from alcohol more difficult.[12]

Barriers to Nicotine and Mental Health Treatment

Multiple reasons exist for the failure to offer nicotine treatment to patients being treated for substance abuse or mental disorders and the related lack of outcome data. In the substance abuse field, barriers includes staff resistance and lack of training.[13,14] Clinicians also express concerns about immediate critical needs such as housing and safety. Historically, there has been a belief in the substance abuse community that the preeminent task during recovery is abstinence from non-nicotine drugs or alcohol, and that other health-related tasks should be delayed until that is achieved.[15] Finally, many substance abuse treatment programs are poorly funded, and treatment of nicotine dependence has not been included in their mandate.[16]

Some of the same barriers exist in mental health settings, including lack of training of providers.[17] The clinical reality sometimes requires that other acute conditions take precedence. Reimbursement for nicotine-dependence treatment is also a concern among clinicians. There is the belief, held by some clinicians, that smoking cessation may cause a reoccurrence of the psychiatric disorder, especially depression.[18] Another important factor may be the relatively low status of nicotine-dependence treatment among mental health policymakers and providers.[16,19,20]

Readiness to Quit Smoking

The success of treatment interventions depends on the interest and readiness of smokers to change behaviors. Several studies have assessed readiness based on the Stages of Change (SOC) model in substance abuse and mental health treatment patients. This model conceptualizes smokers as being in one of five stages with respect to quitting smoking[21]:

1. precontemplation (no intention to change),
2. contemplation (intending to quit in the next 6 months),
3. preparation (considering quitting in the next month with at least one quit attempt in the last year),
4. action (quit smoking for less than 6 months), and
5. maintenance (quit smoking for at least 6 months).

Studies of readiness to change in substance abusers report substantial intentions to quit among both alcohol-treatment patients[22] and methadone-maintenance patients.[23] One study reports that chronic psychiatric patients in a supervised living setting indicated a low level of readiness to quit smoking,[24] but more recent studies present a more favorable picture,[6,7] with levels of interest in quitting approximating those of the general population. The older study included patients with more severe psychiatric disorders, and was conducted at a time when interest in smoking cessation in the general population was lower. Either of these reasons could explain the discrepancies in findings between the earlier study and the later ones.

Treatment Interventions
Treatment of Smokers Who Abuse Substances in Addition to Nicotine

In a meta-analysis, Prochaska et al.[10] reviewed 19 randomized controlled trials that were published between January 1996 and September 2003. Twelve trials included participants currently in treatment for addictions; seven trials included participants who had completed treatment. There was a significant trend toward greater cigarette abstinence at post-treatment for individuals in addiction treatment, with a 12% abstinence

rate for individuals in smoking-cessation interventions and 3% for the smoking treatment-control condition. In the meta-analysis, the more recent studies and the studies that used nicotine replacement therapies (NRT) were more likely to have significant results. For individuals who had completed treatment and were in recovery, at the end of smoking treatment, cigarette abstinence rates were 38% for those provided with a cessation intervention and 22% for those not provided with an intervention, indicating a significant increase in the likelihood of abstinence if an intervention was provided. Cigarette abstinence rates at long-term follow-up indicated a trend toward greater abstinence among the intervention participants, but differences were not significant. The meta-analysis also indicated that providing smoking-cessation interventions did not impede abstinence from alcohol and illicit drugs. At post-treatment assessment, non-nicotine substance-use abstinence rates were 52% in the intervention group and 54% in the comparison condition. At long-term follow-up, non-nicotine abstinence rates were 37% in the intervention group and 31% in the comparison conditions, indicating a slight increase in the likelihood of abstinence from drugs and alcohol among participants receiving a smoking-cessation intervention relative to participants in the control condition. The meta-analysis suggested that there were few studies where differences in substance use among patients in recovery were reported, but those investigations that examined this phenomenon seem to indicate no differences in smoking intervention and control conditions.[10]

A large-scale, controlled clinical trial, published after completion of the meta-analysis, suggests that timing of the intervention may be important. Joseph et al. randomized 499 smokers to concurrent (during alcohol treatment) or delayed (6 months later) smoking intervention.[25] Seven-day point–prevalence abstinence was the primary smoking measure, and the main alcohol outcome measure was 6-month prolonged abstinence from alcohol. Joseph et al. found that participants in the concurrent group were more likely to participate in smoking treatment than those in the delayed group, but that there was no significant difference in cessation rates at 18 months. Six-month abstinence from alcohol and 30-day abstinence from alcohol were consistently worse in the concurrent group than in the delayed group at 6, 12, and 18 months. The authors concluded that their data do not show benefit of concurrent treatment, and that the findings suggest that smoking-cessation interventions are best provided with patients after intensive alcohol treatment.

In summary, it appears that providing smoking-cessation interventions during treatment for alcohol abuse, or drugs of abuse other than nicotine, may increase the probability of cigarette abstinence. Most studies suggest that, contrary to beliefs of some in the clinical community, introduction of smoking treatment

in these settings does not impede abstinence from alcohol or non-nicotine drugs. However, the findings of Joseph et al. suggest the need for further research to insure optimal outcome. Further, overall cigarette abstinence rates are low, especially those obtained when smoking-cessation treatment is offered during the active phase of treatment for the other substance abuse disorder. This further reinforces the need for research to optimize results in these populations.

Treatment of Smokers with Psychiatric Disorders

Most of the nicotine-intervention research with psychiatric patients have been completed with smokers who have a history of major depressive disorder (MDD). The studies have excluded actively depressed individuals. This seems to be a by-product of conducting research in freestanding clinics lacking support for acutely ill patients.

History of MDD

While it is clear that smokers with a history of MDD are helped by additional support, it is less clear whether a particular therapeutic content is more useful than others. Hall et al., among others, hypothesized that cognitive–behavioral therapy (CBT) focused on mood management and thought it to be especially helpful to smokers with a history of depression, however this group was unable to clearly support this hypothesis.[26–28] Later work suggested that CBT may indeed be differentially effective for individuals with a history of recurrent depressive episodes, but this may not be the case for those with a single episode of MDD.[29,30] The reasons for this specificity are not clear. It may be that individuals with a single episode are false positives who have experienced an MDD-like syndrome as a result of illness or life events. Alternatively, it is possible that individuals with recurrent episodes have, over their lifetimes, learned to use skills to manage depression, anger, irritability, and other poor moods, and find the CBT approach consistent with their well-learned coping styles.

One study evaluated nicotine-cessation treatments for smokers who were diagnosed with current depressive disorders.[31] The study recruited 322 subjects from three health maintenance organization's (HMO)-based and one university-based mental health clinics in the San Francisco Bay area. Participants all had unipolar depression. The subjects, who did not have to declare a goal of quitting smoking to be included in the study, were randomly assigned to a stepped-care intervention or a brief contact/referral control. The experimental intervention included motivational counseling using a SOC model, followed by provision of nicotine patches and six sessions of smoking-cessation counseling. Participants were assessed at 3, 6, 12, and 18 months. As hypothesized, the experimental intervention increased

7-day point-prevalence abstinence rates at months 12 (20% vs 13%) and 18 (25% vs 19%). Also, as hypothesized, the intervention made it more likely that heavy smokers would be likely to make a quit attempt, but did not change the probability of a quit attempt for light smokers. The hypothesis that the innovative intervention would increase the probability of participants reporting a goal of total abstinence was supported by the study data, but a hypothesis that smokers with more severe symptoms of depression at baseline would be less likely to attain abstinence than those with less severe symptoms was not supported.

Antidepressant Medications

It seems reasonable to assume that medications would be helpful for smokers with either a history of or current depressive disorders. Two antidepressant drugs are considered effective treatments for tobacco dependence, sustained release bupropion and nortriptyline.[32] However, neither drug has demonstrated greater efficacy for smokers with a history of depressive disorders when compared to smokers without a history of depressive disorders.[28,33–35] Due to a lack of studies, it is unclear whether these findings would hold for currently depressed individuals. The most recent version of the Practice Guidelines[32] suggests that depressed smokers should be prescribed one of these antidepressants, as both smoking and depressive symptoms might be treated. The picture, however, is more complex than this recommendation would suggest because a drug that is optimal for smoking cessation might not be optimal for depression, and the clinician also may have to consider issues that surround the prescription of multiple antidepressants in such cases.

Abstinence from Nicotine and the Recurrence of Depression

The evidence is mixed on the topic of abstinence from nicotine as an influence on depressive episodes. Two large-scale studies have produced conflicting outcomes. Tsoh et al. studied 304 participants and found no differences in rate of occurrence of episodes of MDD as a function of abstinence status over a 1-year period.[36] There was a 14.1% incidence of depressive episodes, independent of history of depression. Among individuals with a MDD history, 23.9% experienced a depressive episode. Among those without a MDD history, 9.7% experienced such an episode. For both history-positive and history-negative subjects, the occurrence of an episode was independent of abstinence status at the time of the assessment. These findings suggest that abstinence and depression are unrelated. There was a higher incidence of depressive episodes than expected, however, therefore care should be taken in considering the relationship between cigarette absence and depres-

sion. It is possible that the process of quitting itself, or even reduction in amount smoked, could precipitate depressive episodes. Further research is needed to address these issues.

In a study of 100 participants, all of whom had a history of MDD, Glassman et al.[37] found that 6% of those smoking (2 people) reported a recurrence of depression, and 31% of those abstinent (13 people) reported a recurrence of depression. These results should be interpreted with caution because of the differential dropout rates of smokers in the two abstinence-status categories; 95% of quitters (42 of 44 people) were followed, as compared with 61% of continuing smokers (34 of 56). The authors reported no significant confounding factors between smoking and abstinent participants, yet the fact remains that a much higher proportion of smokers were not contacted and it is reasonable to assume that individuals who were suffering from depressive episodes were less likely to return for follow-up, and hence that the rate of recurrence among smokers may have been underestimated.

The study of patients being treated for depression reported by Hall et al.[31] was not primarily designed to study the question of recurrence. Nevertheless, the data suggest no evidence of recurrence or worsening of symptoms as a function of cigarette abstinence. There were no differences in outcomes as a function of depression status (recurrent vs single episode), severity of depression, or whether the depression was current or in remission. Smoking status was also unrelated to mental health functioning, days of hospitalization, or changes in severity of suicidal ideation.[38]

Schizophrenia

Two studies suggest that bupropion enhances smoking-cessation rates in nicotine-dependent smokers with schizophrenia, and that it is safe and well tolerated for these individuals. In both studies, the cessation rates were relatively low and relapse rates were high. In a randomized placebo-controlled trial (N=32), George et al.[39] reported higher abstinence rates at treatment discharge using bupropion (50%) compared to the placebo-control group (12%). The rates reported by Evins et al.[40] from a randomized doubleblind placebo-controlled trial (n=53) were lower, with 36% achieving end-of-treatment abstinence rates in the bupropion group and 7% in the placebo groups. The absolute difference in rates between the two studies may reflect the more stringent screening procedures used by George's study, who required reports of motivation to quit smoking on three separate occasions before acceptance into the study. Both studies reported considerable relapse by 6 months from study start, so the significant differences observed at the end of treatment were no longer evident. There have been no breakthrough interventions to suggest how higher absti-

nence rates might be reached with these patients, but given the high smoking rate in individuals with this disorder, such techniques are certainly needed. There are no published studies of smoking cessation in two other populations with a high smoking prevalence: individuals with generalized anxiety disorder and bipolar disorder.

As is the case with depression, the question of worsening schizophrenic symptoms as a function of cigarette abstinence has been raised. The clinical trials reported above found no evidence of this.[39,40]

Integration of Treatment

There is evidence that tobacco-dependence interventions are especially effective if integrated into the mental health services, as opposed to being provided independently. McFall et al.[41] randomly assigned smokers in treatment for post-traumatic stress disorder ($n = 66$) to tobacco treatment delivered by mental health providers and integrated with their mental health care (integrated care) or to smoking services delivered by cessation specialists separately (usual care). Seven-day point-prevalence abstinence was measured at 2, 4, 6, and 9 months after study start. Results indicated that subjects assigned to integrated care were five times more likely than subjects undergoing usual care to be abstinent from smoking across the follow-up assessments. They were also more likely to receive NRT and attended more cessation sessions. Treatment for tobacco dependence was not found to be associated with worsening psychiatric symptoms.

Treatment Settings

Drug-abuse treatment settings themselves may facilitate the initiation of smoking, especially if it is allowed among clients and is prevalent among staff. Kohn et al.[42] studied 749 drug and alcohol treatment patients of a large urban HMO, and assessed smoking status at baseline and 1 year in a subsample ($n=649$) who were retained at 12-month follow-up. They reported that 34.5% (224) of the sample were nonsmokers at both points, and 52.7% (342) were smokers. Fifty-three (8.2%) had quit during the course of the year, but 4.6% (30) reported relapsing or initiating smoking. Of these 30 individuals, 11 were classified as never-smokers at the baseline interview. While this is a small number, it raises the possibility that substance abuse treatment settings with their high smoking rates among patients and staff may induce smoking in some nonsmokers. An effort to prevent initiation within treatment is appropriate.

Prevention

There have been no studies of primary prevention for tobacco dependence for individuals with substance abuse or mental health disorders. In part, this may stem from the fact that many of these disorders develop concurrently with tobacco dependence or after the initiation of smoking. This is not the case with at least one disorder where high rates of cigarette smoking have been reported: Attention Deficit Hyperactivity Disorder (ADHD), a disorder that is most commonly diagnosed in children aged 7 and 9 years. Rates of smoking for adolescents with ADHD are two to three times higher than those for adolescents without ADHD.[43,44] Furthermore, there is evidence that adults with childhood ADHD may have more difficulty in quitting smoking than the general population.[45]

Another identifiable group who may be at high risk is children of individuals with alcohol and other substance abuse disorders. For example, Schuckit et al.[46] reported in a prospective 20-year study that middleclass sons of individuals with alcohol problems (N=249) were more likely to be recent smokers than the controls, whether or not they had an alcohol problem themselves. Comparable studies have not been completed on children of those with mental disorders.

Summary and Recommendations

Research on smoking cessation in the treatment of substance-abusing individuals and individuals with mental health disorders is very much in its infancy. Core questions, such as whether the interventions used in the general population work in these populations in a similar fashion, have yet to be fully addressed. Questions of timing, tailoring of the intervention to the specific problems of mental health and substance abuse patients, and the possible effects of cessation on mental health problems need study. Moreover, research on targeted prevention efforts is seriously lacking.

Given the high prevalence of tobacco dependence in populations with psychiatric and substance abuse disorders, studies of effective treatment interventions for these populations are greatly needed. Smokers with substance abuse and psychiatric disorders appear willing to quit. However, with respect to individuals who abuse non-nicotine drugs in addition to tobacco, the evidence suggests that provision of tobacco-dependence treatment can increase cigarette abstinence rates, whether provided during treatment or during the recovery period. There is also little evidence that so doing conflicts with abstinence from alcohol or other drugs.

With respect to other psychiatric illnesses, the existing data are unevenly distributed and there are not enough data to form a model of effective treatment. Data indicate that increased treatment support may be differentially effective for smokers with a history of MDD, and that it is likely that individuals with recurrent episodes are differentially helped by cognitive behavioral approaches that focus on mood management. The two antidepressants that have been found to be effective

for the treatment of tobacco dependence, sustained-release bupropion and nortriptyline, are effective for smokers with a history of depression, but there is no evidence that they are more helpful in that group of smokers than with individuals without such a history. There have been case studies suggesting that smoking cessation is related to recurrence of MDD, but the large-scale studies that addressed this issue have provided mixed results. However, MDD is a chronic relapsing disorder, so awareness of the possibility of recurrence is always prudent. There are few studies that address the treatment of smoking in schizophrenic patients. They suggest that the pharmacologic treatments that work in the general population also will have some effect with schizophrenic patients, but the magnitude of the effects is smaller. There is no evidence that cessation exacerbates schizophrenic symptoms. Cessation interventions remain virtually unstudied in some groups with high prevalence rates, bipolar disorder is a case in point.

There is also some evidence that integration of cessation treatment into mental health treatment may be especially effective, but education and well-designed services and organizational research are needed to overcome multiple barriers to integrating smoking cessation into substance abuse and mental health treatment. Prevention studies targeted at special populations do not exist. However, there are some high-risk populations—children with ADHD, children of diagnosed drug abusers, and perhaps individuals in substance abuse treatment—who might be excellent targets for prevention research.

The strongest recommendation arising from the current literature is, of course, that more research on treatment interventions in these populations is needed. Until such research is completed, it is reasonable to recommend that the field offer interventions that parallel those in the general population. The magnitude of the results may vary, but they exceed the impacts obtained by no treatment and there is little, if any, evidence that harm may be done. While clinical trials in freestanding clinics are of interest to develop innovative interventions, health services research on how best to integrate interventions in substance abuse and mental health treatment are needed. Targeted studies of prevention are possible and should be completed.

Implications for the Field of Tobacco Dependence

The major implications of the findings of this review for the general field of tobacco dependence are fourfold. First, as discussed in the section on readiness for treatment, comorbid smokers appear to have substantial readiness to quit smoking, and they are willing to enter into intervention studies. The field cannot and should not ignore these smokers with the rationale that they are unwilling to quit smoking, or do not have the

motivation to participate in treatment. A second issue is the extent to which special interventions which are targeted at comorbid smokers are needed, or whether these populations will be well served by those interventions that are used in the general population. Data are only beginning to be accrued that might answer this question. For example, Hall et al.[31] obtained abstinence rates in depressed smokers that were comparable to those obtained in the general population when comparable interventions had been implemented.[47,48] In contrast, well-controlled studies of bupropion in smokers with schizophrenia have resulted in abstinence rates better than placebo, but the overall rates were lower than those found in the general population and the effect in smokers with schizophrenia were not maintained at long-term follow-ups.[49,50] Again, this had not been the case in general population studies.[51] It is not known whether this is due to the heavy smoking and resulting high level of dependence that characterizes smokers with schizophrenia[49,50] or to factors unique to the disease itself, independent of level of dependence. It is possible that some, but not all, treatments used in the general population will generalize well to comorbid smokers. Data relevant to this issue are important to the general field of tobacco dependence and have implications for the more general question about the importance of tailoring treatments to specific subpopulations.

A third issue is the relative importance of comorbid smokers to the field in general. Much has been written about the "hardening" of smokers, in the sense that smokers are becoming less likely to quit smoking.[52–55] There is controversy about definitions of the hardcore smoker[53,55] and to what extent this phenomenon should dictate policy.[55] However, most writers appear to agree that hardcore smokers, such as those with psychiatric disorders, may constitute a growing, if small, proportion of the population.[55] One might well argue with the assumption that this proportion is, and will remain, small, however. This may be the case if one limits the definition of psychiatric disorder to serious mental illness, particularly schizophrenia. However, an estimated 26.2% of Americans aged 18 and older suffer from a diagnosable mental disorder in a given year.[56] Another 8.5% suffer from alcohol-related disorders,[57] and 10.3% suffer from other non-nicotine substance abuse disorders at some time in their lives.[58] Lasser's data[2] indicate that both current and historic mental disorders in general, not just serious mental illness, predict lower smoking-cessation rates. Therefore, one can argue that this population represents a substantial proportion of smokers, not a small proportion, and that this proportion may increase in years to come. Thus, the field may find itself increasingly called on to develop effective treatment strategies for individuals with psychiatric and non-nicotine substance abuse disorders. There is a final implication from the develop-

ment of successful treatment strategies and identification of unsuccessful ones. That is the development of a more general understanding of nicotine dependence and the comorbid disorder.

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Smoking Cessation

A Critical Component of Medical Management in Chronic Disease Populations

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Abstract: Many innovative and effective smoking-cessation treatments, both behavioral and pharmacologic, have been developed over the past several decades. However, these treatments traditionally have been developed for use with populations of healthy smokers. Despite the disease management implications, efforts to design and evaluate cessation interventions targeting smokers diagnosed with chronic diseases are reported infrequently in the literature. The purpose of this paper is to provide a brief overview of the evidence linking continued smoking to disease progression and adverse treatment outcomes across a range of common chronic diseases: cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), diabetes, asthma, cancer, and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS). Where studies are available, the efficacy of smoking-cessation interventions specifically developed or applied to these patient populations is reviewed. Finally, limitations and gaps in smoking research and treatment with chronically ill patients are discussed, and future research priorities are recommended.
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Introduction

For many years, smoking-cessation efforts have been aimed primarily at healthy people in the general population as a form of primary prevention. Individuals at elevated risk for certain diseases, or who had already experienced an illness, e.g., cardiovascular disease (CVD) or early chronic obstructive pulmonary disease (COPD), were targeted as well. However, smoking and tobacco cessation among people with other types of severe chronic illness has received less attention from healthcare practitioners and researchers. This lack of emphasis may be attributable to the focus on acute treatment of a life-threatening illness, a potential or actual high mortality rate, lack of cessation treatment tailored to these populations, and the perceived lack of relevance of smoking to treatment outcome and survival. Two major examples are cancer and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), both of which have seen increased survival over the last decade. While empirically-validated treatments for smoking cessation are available in the general population, it is critical to evaluate their use for patients with chronic illness and to determine whether important modifications must be made based on disease-specific issues.

In this article, findings involving smoking-related outcomes are integrated across a range of chronic illnesses: CVD, COPD, diabetes, asthma, cancer, and HIV/AIDS. First, a brief overview is provided of the evidence linking continued smoking to disease progression and adverse treatment outcomes for each illness specified. The effectiveness of smoking-cessation interventions targeting these patient groups is addressed as findings are presented from relevant empirically-tested cessation interventions. Finally, limitations and gaps in smoking research and treatment with chronically ill patients are identified and discussed. This article is organized by disease category to highlight the considerable variability in the scope and strength of the scientific literature on these topics for each group. Considering the breadth of illnesses highlighted, exhaustive coverage of all relevant smoking-related literature is beyond the scope of this article. The focus here is on presenting seminal work and critical studies to elucidate key outcomes and research issues.

Cardiovascular Disease

Cardiovascular disease (CVD) encompasses a number of diseases, including coronary heart disease (CHD), the leading cause of myocardial infarctions (MIs); cerebrovascular disease (stroke); aortic aneurysm; and peripheral vascular disease (PVD). Burns[1] reviews a body of evidence related to continued adverse effects of smoking after the onset of documented disease and concludes that, overall, continued smoking results in

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disease progression, recurrent events, and higher mortality, and smoking cessation reduces disease risks over time, depending on the specific condition. Smoking cessation after MI or in angiographically-documented coronary artery disease leads to significantly lower rates of re-infarction within 1 year, compared to continued smoking, and remains much lower over time. Among those with CHD, continued smoking was associated with an increased risk for sudden coronary death. Following coronary artery bypass surgery, continued smoking at 5 years is associated with increased risk for MI, angioplasty, and development of angina. Cessation of smoking following bypass surgery resulted in a 10-year survival of 84% versus 68% among continuing smokers.[2] In patients with PVD, continued smoking is associated with much lower rates of improvement with medical management alone compared to nonsmoking patients, higher rates of amputation compared to quitters, and higher rates of obstruction following surgery.[1] The Cochrane Collaboration[3] meta-analysis (20 studies) estimated the magnitude of risk reduction when a patient with CHD stops smoking; it reported a pooled crude relative risk (RR) of 0.64 (0.58–0.71), representing a 36% reduction in all-cause mortality in former smokers compared to continuing smokers.

In patients with CVD, empirically-tested cessation interventions primarily have been nurse-delivered and conducted with hospitalized men. These studies have demonstrated mixed outcomes prompting disagreement regarding intervention efficacy in this patient population. Barth et al.[4] recently reviewed 19 randomized controlled trials of psychosocial interventions for smoking cessation in patients with CHD. Across intervention studies, significant positive effects on abstinence were detected after 6 to 12 months (odds ratio [OR]=1.66; 95% confidence interval [CI]=1.24–2.21). Little difference was found when comparing specific treatment strategies such as individual or group therapy, telephone counseling, or provision of self-help materials. Treatment intensity emerged as a critical factor such that brief interventions without follow-up contact did not appear effective (OR=0.092; 95% CI=0.70–1.22), while more intensive intervention showed significantly increased quit rates (OR=1.95; 95% CI=1.61–2.35).

As few trials have included women, a recent study by Froelicher et al,[5] conducted exclusively with hospitalized women diagnosed with CVD, warrants attention. In this randomized controlled trial, 277 women were randomly assigned to receive usual care (i.e., strong physician advice, self-help materials, and a list of community resources) or intervention (i.e., strong physician advice, nurse-managed cognitive behavioral relapse prevention intervention at bedside, provision of nicotine replacement therapy [NRT], telephone contact after discharge). Follow-up evaluations were conducted at 6, 12, 24, and 30 months. Results showed high

nonsmoking point prevalence rates (ranging from 40% to 50%) in both groups at all follow-up points, with trends somewhat greater for the intervention group compared to usual care. Although the protocol only included the provision of NRT for eligible intervention group participants, it is of some interest that comparable rates of NRT use were detected in both groups. Significant intervention effects were found for smoke-free time, such that intervention participants demonstrated a significantly longer interval to relapse compared to participants in the control group.

The use of standard pharmacologic treatments (i.e., NRT and bupropion) for smoking cessation has been somewhat controversial in patients with CVD. For nicotine replacement products, safety issues center on the hemodynamic effects of nicotine, which can include an increase in heart rate and blood pressure and increased myocardial contractility.[6] Adrenergic stimulation associated with bupropion use has raised concerns about increased myocardial work and potential blood pressure increase.[6] However, mounting evidence supports the safety of NRT and bupropion use in this patient group. Across randomized controlled clinical trials and efficacy studies, NRT use has not been found to affect the frequency of adverse cardiac events among patients with CVD.[6,7] Additional data have revealed the lack of association between the nicotine patch and acute cardiovascular events even in patients who continue to smoke intermittently while on the nicotine patch.[7] Although less data are available on the use of bupropion in patients with CVD, studies show that bupropion does not affect heart rate, cardiac conduction, and myocardial function.[6] A large, randomized, placebo-controlled multicenter trial of bupropion in 626 patients with CVD found bupropion to be well-tolerated by participants and reported a safety profile for the drug similar to that observed in the general population.[8] In their review of the literature, Joseph and Fu[6] point to the need for data on the safety of bupropion use in patients with existing cardiac disease as well as additional evaluation of the safety of pharmacologic agents in patients with acute or unstable cardiovascular conditions.

Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) describes a range of conditions involving damage to the lungs, which arises primarily from the inhalation of tobacco smoke: chronic obstructive bronchitis, emphysema, and chronic airflow obstruction. Permanent cessation of smoking by individuals with early COPD (mild to moderate airway obstruction) dramatically reduces the progression to clinically serious lung disease as found in the Lung Health Study.[9] Intervening once lung disease has become disabling results in a slowing in the rate of decline of lung function, but the benefits

are more limited in terms of symptomatology.[10] Mortality risk from COPD declines following smoking cessation compared to continued smoking, but this decline is less than for heart disease and lung cancer and remains elevated in former smokers even after 20 years of abstinence.[10]

In a recent review of randomized controlled trials of smoking-cessation interventions conducted with individuals with COPD, Wagena et al.[11] concluded that combination treatment (psychosocial plus pharmacologic intervention) is superior to no treatment or psychosocial intervention alone. This conclusion was based largely on the results of the Lung Health Study, a multicenter clinical trial with 5887 participants who were followed for up to 15 years. The cessation intervention evaluated in this large-scale study was a 10-week program including a strong physician message, 12 group sessions using behavior modification, and nicotine gum. Intervention participants were further randomized to receive either an inhaled bronchodilator or a placebo inhaler. These two intervention groups were compared to a usual care condition. The cessation program with or without the use of a bronchodilator was associated with cumulative reduced decline in lung function at 5-year follow-up. Combining results from the two intervention groups, significant differences in quit rates also were found at 5-year follow-up (21.7% intervention group vs 5.4% usual care, $p<0.001$).[12]

A recent randomized controlled study not included in previous reviews of the literature was conducted by Hilberink et al.,[13] who compared a minimal intervention strategy to usual care. Treatment components of the intervention varied based on the participant's motivational stage of change but generally included educational materials, behavioral strategies, and pharmacotherapy recommendations. Significant differences were found in quit attempts between the two groups (44.9% intervention vs 36.5% control, $p=0.003$) as well as in actual cessation at 6-month follow-up (16.0% intervention vs 8.8% control, $p=0.046$). Of additional interest is the lack of differences in abstinence rates based on motivational stages, suggesting that this intervention strategy appeared to be equally effective in patients with different levels of motivation to quit smoking.

Particular attention has been given to evaluating the safety and efficacy of pharmacotherapy for patients with COPD. Two large clinical trials have been conducted to evaluate the use of bupropion SR with this patient population. Tashkin et al. conducted a doubleblind randomized controlled trial comparing bupropion to placebo in 404 patients with mild to moderate COPD.[14] Bupropion was well-tolerated and associated with significantly higher rates of continuous abstinence throughout the 12-week treatment phase and at the 26 week follow-up visit. At the 6-month follow-up, significantly more participants receiving bupropion remained abstinent than those receiving placebo (16% vs 9%, $p=0.04$). Wagena et al.[15] conducted a randomized trial to assess the efficacy of bupropion and nortriptyline among smokers with or at risk for COPD. Among those with COPD, higher prolonged abstinence rates were found with both bupropion and nortriptyline when compared to placebo, but only the difference between the bupropion and placebo groups was statistically significant (27% vs 8.3%, $p=0.02$). Among participants at risk for COPD, differences in prolonged abstinence rates between groups were much smaller and not statistically significant.

Diabetes

Both cross-sectional and prospective studies have consistently shown higher risk for micro- and macro-vascular disease, as well as for premature mortality in diabetic patients who smoke.[16] Among adults with diabetes, smoking is associated with increased death from CHD, diagnosis of coronary artery disease, stroke, nephropathy and neuropathy. Damage and constriction of blood vessel by smoking can lead to exacerbation of foot ulceration, blood vessel disease, and lower extremity amputation.[17] The increased cardiovascular burden of diabetes among patients who smoke needs to be emphasized by healthcare providers; advice to quit is delivered to only about half of the smokers with diabetes.[16,18,19] Specific factors identified as contributing to difficulties in achieving long-term abstinence from smoking in the diabetic patient include smoking initiation in adolescence, problems of weight management, negative affect, and low motivation for cessation at the time of hospitalization.[16]

Data on the efficacy of smoking-cessation interventions for individuals with diabetes are not readily available because large-scale studies including patients with diabetes do not report results separately for this group. However, several controlled trials targeting patients with diabetes have been published recently. Results were mixed, with positive effects found in studies with larger sample sizes. Canga et al.[20] conducted a randomized clinical trial with 280 diabetic smokers, comparing a nurse-delivered intervention with scheduled follow-up to usual care. The intervention consisted of an initial face-to-face interview, optional NRT, and a follow-up support program. Significant intervention effects on cessation were detected at 6-month follow-up (17% nurse-intervention vs 2.3% usual-care quit rate, $p<0.001$). Among participants who continued smoking, significant intervention effects were also found for decreased cigarette consumption. Positive intervention effects also were found in a study comparing a nurse-delivered motivational interviewing intervention in a control condition (i.e., advice letter).[21] Participants included 211 smokers with diabetes from primary care intervention centers and 140 smokers with diabetes from primary

care control centers. Intervention participants self-selected to receive either eight group sessions ($n=47$) or telephone interview and follow-up ($n=164$). Despite these variations, significant differences in quit rates were found between participants in the intervention centers compared to the control centers (20% vs 7%, $p<0.01$) at 1-year follow-up. These findings are limited by the lack of biochemical verification of smoking status and the nonrandomization of centers to experimental condition or participants to intervention condition.

In a final study, motivational interviewing and phone counseling were integrated into a standard diabetes self-management training program for current smokers with diabetes.[22] The smoking-cessation intervention consisted of a face-to-face counseling session and an additional three to six telephone counseling sessions (based on the participant's readiness to quit smoking). Although a trend toward a higher rate of abstinence was found at 3-month follow-up for intervention participants ($n=57$) compared to control participants receiving standard care ($n=57$), there was no significant difference in group smoking-cessation rates at 6 month follow-up. While this study supported the feasibility of incorporating a smoking-cessation intervention into a diabetes self-management program, it appears further research is needed to determine the most effective means of reducing tobacco use among these high-risk chronically ill patients.

Asthma

Although factors affecting the development of asthma are poorly understood, active smoking and exposure to secondhand smoke are known to trigger and aggravate asthmatic symptoms.[23,24] Previous studies have linked smoking with more frequent attacks, more severe symptoms, higher hospitalization rates, and accelerated decline in lung function.[24–27] Adverse outcomes associated with exposure to secondhand smoke include increased symptoms, poor quality of life, reduced lung function, and increased hospitalizations and emergency visits.[24,26] Research also suggests that the effectiveness of treatments for asthma may be compromised by smoking. Tyc and Throckmorton-Belzer[28] reviewed research demonstrating poor responsiveness to inhaled or oral steroid treatments based on cigarette dose-dependent inflammatory responses and altered cytokine regulation in the airways of adult smokers.

Despite the negative health effects of smoking on asthma, smoking prevalence among individuals with this chronic illness consistently has been shown to be similar to or higher than the general population. Prevalence of current smoking among asthmatics ranges from 17% to 35% in different studies, with the highest rates found among those presenting at emergency rooms for acute attacks.[24–26,28] Empirically-tested cessation studies directly targeting individuals with

asthma are lacking. Available research with this patient population focuses on reducing exposure to second-hand smoke rather than intervening with active smoking. As such, no conclusions can be drawn about the effectiveness of smoking-cessation treatment for this chronically ill patient population.

Cancer

Tobacco use, including exposure to secondhand smoke, has been implicated as a causal or contributory agent in an ever-expanding list of cancers, including lung, oral cavity, pharynx, esophagus, pancreas, urinary bladder, renal pelvis, nasal cavities and nasal sinuses, stomach, liver, kidney, uterine cervix, and myeloid leukemia.[29] Independent of the etiologic effects of tobacco carcinogens in numerous cancers, a growing literature also documents the direct and indirect adverse effects of smoking on oncologic treatment efficacy (short- and long-term outcomes), toxicity and morbidity, quality of life (QOL), recurrence, second primary tumors (SPT) and survival time.[30–33]

Population-based estimates of smoking prevalence across cancer type suggest that smoking rates among individuals surviving cancer are similar to those without a history of cancer (20.2% vs 23.6%).[34,35] One notable difference is that significantly elevated rates of current smoking (42.6%) have been found among young adults with cancer (18–40 years) compared to noncancer controls (26.5%).[34] Beyond these data, research on the smoking behaviors of cancer patients tends to focus on individuals with smoking-related tumors. Across different studies, rates of current smoking among patients with head and neck or lung tumors at diagnosis has ranged from 40% to 60%.[32,36,37] Research suggests that motivation and interest in smoking cessation greatly increase in people with smoking-related tumors following cancer diagnosis.[38–40] Particular emphasis has been given to promoting cancer diagnosis as a "teachable moment" for healthcare providers to intervene and assist with smoking cessation.[31,32]

While many of the same factors that influence cessation in the general population (e.g., nicotine dependence, readiness to quit, age) also have been found to influence cessation in cancer patients,[38] a variety of unique factors must be taken into account when delivering cessation treatment to this patient population. Previously identified challenges of tailoring cessation interventions to meet the particular needs of individuals with cancer include: (1) particularly high levels of nicotine dependence as evidenced by long histories of heavy tobacco use with continued smoking under life-threatening circumstances, (2) pressure for abrupt and immediate cessation to promote improved cancer treatment efficacy, (3) significantly elevated levels of psychological distress, which are known to impede smoking-cessation efforts, (4) the delayed nature of relapse compared to smokers in the general

population, (5) physical limitations imposed by disease and treatment which can affect recommendations regarding exercise regimens and dietary change, and (6) medical contraindications to certain types of NRT and other pharmacotherapy.[31,32]

Empirically-tested cessation interventions with cancer patients have been conducted in various settings, ranged in intensity, and showed mixed results. Gritz et al.[38] conducted the first randomized trial of a surgeon-/dentist-delivered intervention for 186 newly diagnosed patients with head and neck cancer. The intervention consisted of strong personalized advice to stop smoking, a contracted quit date, tailored written materials, and booster advice sessions, and was compared to a minimal-advice control condition. At 12-month follow-up, 70.2% of all participants were continuous abstainers, regardless of treatment condition. Although no significant differences were found between the enhanced and minimal-advice conditions, the high sustained quit rates across all participants were quite promising and novel. These findings demonstrate the value of systematic brief advice to stop smoking for head and neck cancer patients, which can be readily incorporated into a standard treatment regiment.

An array of empirically-tested nurse-delivered cessation interventions have been conducted with hospitalized cancer patients. These studies included patients with varying cancer diagnoses and contained small samples ranging from 15 to 80 patients. The typical intervention employed in these studies consisted of three in-hospital visits, the provision of educational materials, and five post-discharge telephone calls. Across four separate studies, abstinence rates varied considerably within the intervention group at 6-week follow-up (21%,[41] 40%,[42] 64%,[43] 75%[44]). Among the studies including a control condition, abstinence rates ranged from 14% to 50%.[41,43,44] Generally, higher quit rates were found in studies with a higher percentage of head and neck cancer patients.

Larger-scale smoking cessation studies conducted more recently with cancer patients emphasize the need for early intervention and reinforce the particular benefits of cessation treatment for patients with smoking-related tumors. In two separate studies conducted at the Mayo Clinic Nicotine Dependence Center,[45,46] a matched-pair design was used to retroactively analyze abstinence rates at 6-month follow-up for patients with specific smoking-related cancers compared to matched controls. Despite divergent findings regarding overall intervention effects, both studies found that duration of time between cancer diagnosis and smoking-cessation treatment significantly affected tobacco use outcome. Significantly higher abstinence rates were found for both lung and head and neck cancer patients treated within 3 months of diagnosis compared to those treated more than 3 months after diagnosis. In another trial coordinated by the Eastern Cooperative Oncology Group, cancer patients (N=432) were randomly assigned to physician-based smoking cessation (including brief advice, optional NRT, and written materials) or usual care (unstructured advice from physicians).[47] Although no significant differences were found at 6- or 12-month follow-up between intervention and control participants, cancer diagnosis emerged as a significant predictor of abstinence. Consistent with other studies, patients with head and neck or lung cancer were significantly more likely to have quit smoking compared to patients with tumors that were not smoking-related.

As cessation research with cancer patients continues to expand, Emmons et al.[48] recently conducted a randomized control trial of a peer-based telephone-counseling intervention versus self-help intervention for young adult survivors of pediatric cancers (N=796). Childhood cancer survivors smoke at rates that are only slightly lower than the general population, and it is important to recognize that the health consequences of smoking are much greater for these cancer survivors compared to the general population. The cessation intervention was delivered by a trained childhood cancer survivor and included six calls, tailored and targeted written materials, and optional NRT. Significantly higher quit rates were found in the counseling group compared to the self-help group at both the 8-month (16.8% vs 8.5%, $p < 0.0003$) and 12-month (15% vs 9%, $p \leq 0.01$) follow-up.

HIV/AIDS

The first decade of the highly active antiretroviral therapy (HAART) era has witnessed a significantly improved prognosis for people infected with HIV. The risk of many AIDS-related diseases, such as non-Hodgkin's lymphoma, Kaposi sarcoma, and *Pneumocystic carinii*, has decreased significantly while life expectancy has increased significantly.[49,50] This trend of improved survival along with relatively stable HIV incidence rates has resulted in an ever-growing population of people living with HIV/AIDS. In fact, recent estimates indicate that more than one million individuals in the United States are living with HIV/AIDS, and an additional 40,000 Americans are infected each year.[51,52] While the improved health outcomes attributable to HAART are certainly positive, other potential health risks, such as cancer and CVD, are now becoming more evident.[53–55] Thus, further efforts to reduce the risk of these conditions in the ever-growing HIV-positive population are critically needed.

Cigarette smoking is not only a highly prevalent behavior among people living with HIV/AIDS, it is also associated with numerous disease- and treatment-related adverse outcomes. Data from several published reports indicate that the prevalence of current smoking within the HIV-positive population is between 50% and

65%.[56–58] This elevated prevalence is especially disturbing given the association of smoking with several AIDS-related diseases, including pulmonary infections, oral diseases, and malignancies.[49,59] While the increased risk of CVD among current smokers is well-established, HIV-positive smokers appear to be particularly at risk. Existing evidence indicates that prolonged use of protease inhibitors, a crucial component of HAART, is associated with metabolic changes. For example, individuals on prolonged HAART regimens frequently experience increases in total cholesterol, triglycerides, and insulin resistance; a reduction in high-density lipoprotein cholesterol; and lipodystrophy.[60] Thus, the incidence of CVD has been increasing among the HIV-positive population in the HAART era.[61] Because strict adherence to HAART regimens is required to prevent HIV disease progression, it is vital that modifiable risk factors for CVD, such as smoking, be targeted for intervention.

A final area of concern that has received growing attention in recent years is the significantly increased risk of malignancy among people with HIV/AIDS. HIV-associated malignancies, such as anal and cervical cancer, are observed significantly more frequently among HIV/AIDS patients who smoke.[62,63] Other cancers commonly associated with cigarette smoking, such as lung and head and neck cancers, are observed more frequently among HIV-infected smokers compared to non-infected smokers, indicating a synergistic relationship between smoking and HIV.[64,65] In fact, because of the growing incidence of lung cancer among people living with HIV/AIDS, some researchers have suggested that a reclassification of lung cancer as an AIDS-related malignancy be considered.[66,67]

While the true attributable risk of cigarette smoking in the HIV-positive population would be difficult to estimate due to the numerous disease- and treatment-related interrelationships, it appears highly likely that reducing smoking prevalence would result in better disease management and increased survival times. Recently published findings from the WIHS (Women's Interagency HIV Study) cohort support this view: women who were current smokers experienced significantly poorer viral and immunologic response to HAART, and significantly higher risk of death.[57] A striking trend was also observed by Lewden and colleagues.[53] A detailed review of the causes of death among HIV/AIDS patients reported from various hospital wards in France indicated that cigarette smoking was reported in almost 75% of cancer-related deaths. This finding led the authors to conclude that the prevention of non-AIDS malignancies (especially lung cancer) is among the most important priorities for HIV/AIDS management.

Despite the extremely high prevalence of current smoking among people living with HIV/AIDS, and the elevated risk of cancer, CVD (and other adverse health outcomes) and mortality confronting HIV-positive smokers, there have been few efforts to target this population for smoking-cessation treatment. One of the reasons for this lack of effort is, most likely, the historically poor prognosis of HIV/AIDS. For example, findings from a focus group study suggested that HIV-positive smokers tended to believe that they would not live long enough to experience the adverse consequences of smoking.[68] Barriers to traditional forms of smoking cessation treatment also may partially explain the lack of research. In a small study designed to identify potential treatment barriers, Lazev and colleagues[69] found that although interest in cessation treatment was high, lack of access to a working telephone, a high number of household moves, and lack of transportation greatly limited the ability of the HIV-positive population to participate in traditional behavioral-based interventions. However, a small feasibility trial, consisting of peer-led counseling sessions and the nicotine patch, does suggest that targeting HIV-positive individuals able to participate in a traditional Public Health Service (PHS) treatment regime can result in high cessation rates, with 50% abstinent at 8-month follow-up.[70]

Another recently published pilot study attempted to overcome some of the barriers to smoking-cessation treatment in order to reach a more representative sample of HIV-positive smokers. In this trial, the study sample (N=95) consisted of consecutive patients receiving care at a large, inner-city HIV/AIDS clinic who were proactively screened for smoking. Current smokers were then recruited to participate in the trial, which was designed to compare a standard-care treatment approach to a cell phone-delivered intervention. Per PHS recommendations, the standard-care group received physician advice to quit, written materials, and nicotine patch. Participants in the cell phone-delivered intervention received the standard-care elements plus eight proactive counseling sessions delivered via cell phone. Outcome analyses conducted with 3-month follow-up data indicated that participants randomized to the cell phone group were significantly more likely to have quit smoking compared to participants receiving only the standard-care treatment (36.8% vs 10.3%, $p<0.01$).[71]

While preliminary, findings from this pilot trial are encouraging. A larger efficacy trial of the cell phone treatment is currently underway, consisting of more comprehensive assessment of potential treatment mediators/moderators and long-term (12-month) outcome assessments. In addition to this ongoing trial, three other smoking-cessation trials are targeted to the HIV-positive population: (1) Motivation and patch treatment for HIV-positive smokers (5R01DA012344); (2) Motivating HIV-positive Latinos to quit smoking (5R01DA018079); and (3) Smoking treatment in HIV

clinical care settings (K23HL073873).[72] Findings from these trials have not yet been published.

Research Priorities

Future studies conducted with these populations of chronically ill patients should utilize evidence-based interventions in order to maximize the likelihood of identifying effective treatments. The U.S. Department of Health and Human Services (USDHHS) Smoking-Cessation Clinical Practice Guideline[7] is currently under revision and will next be published in 2008. Hopefully, it will provide further guidance on the treatment of these special populations. Many studies in the literature, to date, are not theory-driven, are based on less rigorous methodology, have inadequate sample sizes and thus lack statistical power, or are exploratory in nature. Clearly, a stronger body of literature is needed to guide treatment recommendations.

One remaining question is whether interventions evaluated in the general population of smokers require modification or tailoring for chronically ill people and to what degree. Physical limitations, disease-related issues, and medication management obviously need to be considered, but beyond these, what might be important? Some suggestions include comorbidities (physical, psychological, and substance-related), family involvement (and treatment of smoking among other family members), access to treatment, role of the medical provider and treatment team, and specially tailored materials. Related to tailoring is the timing of the intervention and the identification of the "teachable moment." It may be possible to deliver the smoking-cessation intervention concurrent with diagnosis and lasting through initial stages of medical treatment. Surgical treatments provide a substantive period in the hospital, during which smoking is not possible, but that is not true of all medical treatments (e.g., radiation or chemotherapy) and treatment may need to extend into the period of physical recovery to prevent relapse. It is also not known whether people with chronic illnesses who fall into population subgroups distinguished by gender, race/ethnicity, low socioeconomic status (SES), and other underserved groups will have greater difficulty quitting and may benefit from tailoring.

Because those people who continue to smoke while suffering from chronic illness are likely to be more nicotine-dependent and have more comorbidities than those who have quit, combined pharmacologic and behavioral interventions may be particularly important. In healthy populations, standard treatment courses of pharmacotherapy (i.e., NRT, antidepressants) double quit rates over counseling alone[7]; however, relapse over time is a universal problem that is particularly important to address in ill populations. It will be important to test combinations of agents, extended treatment to sustain abstinence and prevent relapse, and to explore new agents once they are found efficacious in healthy smokers. Clinical acumen will be critical to evaluating potential contraindications due to disease or to medical treatment agents. As in the case of nicotine replacement and CVD, careful testing and evaluation may show benefit where initially there are safety concerns.

Research into provider-level interventions, including best practices and broad healthcare specialty involvement, is clearly indicated in this area. Once efficacious and effective interventions have been identified, these need to be widely disseminated in the appropriate communities of providers and healthcare systems. It would be important to see healthcare system and policy-based interventions supporting smoking cessation in chronically ill populations, providing free coverage of services and medication, and evaluation of care delivery. Equally important for both patients and families is the reduction of secondhand smoke exposure, the disease burden of which was recently definitively documented in the 2006 Surgeon General's Report.[23]

Conclusion

Smoking cessation is a critical aspect of the management of many chronic diseases, both in terms of treatment outcome, progression of disease, comorbidities, quality of life, and survival. The evidence, insofar as it exists in the literature, has been summarized for CVD, COPD, diabetes, asthma, cancer, and HIV/AIDS. "Spontaneous" smoking cessation and quits prompted by healthcare provider advice most likely occur in individuals with less nicotine dependence and/or without comorbid conditions. The literature indicates that those people who continue to smoke may be more challenging to treat than healthy populations. Populations with chronic disease may have specific medical and psychosocial issues that must be addressed in targeted and tailored smoking-cessation interventions. However, for some conditions, successful treatments have reduced significantly smoking prevalence compared to controls and improved the health of patient populations. There are many gaps in the literature and it appears that far too little attention has been focused on the smoking behavior of these growing populations of individuals living with chronic disease. To date, the literature is insufficient to draw firm conclusions on effective smoking-cessation treatments for most conditions. More research is strongly warranted and should be highly prioritized. Some areas of research are relatively new, such as smoking cessation for cancer patients/survivors and people living with HIV/AIDS. These need to be pursued vigorously because of the emerging evidence on benefits to health and quality of life. It is hoped that this article will provide a stimulus to researchers, funders, and policymakers.

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