AMERICAN THORACIC SOCIETY DOCUMENTS

An Official American Thoracic Society Research Statement: Current Understanding and Future Research Needs in Tobacco Control and Treatment

Frank T. Leone, Kai-Hakon Carlsen, Patricia Folan, Karen Latzka, Alfred Munzer, Enid Neptune, Smita Pakhale, David P. L. Sachs, Jonathan Samet, Dona Upson, and Alexander White; on behalf of the ATS Tobacco Action Committee

This official Research Statement of the American Thoracic Society (ATS) was approved by the ATS Board of Directors, April 2015

Introduction: Since the mid-20th century, the scientific community has substantially improved its understanding of the worldwide tobacco epidemic. Although significant progress has been made, the sheer enormity and scope of the global problem put it on track to take a billion lives this century. Curbing the epidemic will require maximizing the impact of proven tools as well as the development of new, breakthrough methods to help interrupt the spread of nicotine addiction and reduce the downstream morbidity.

Methods: Members of the Tobacco Action Committee of the American Thoracic Society queried bibliographic databases, including Medline, Embase, and the Cochrane Collaborative, to identify primary sources and reviews relevant to the epidemic. Exploded search terms were used to identify evidence, including tobacco, addiction, smoking, cigarettes, nicotine, and smoking cessation. Evidence was consolidated into three thematic areas: (*1*) determinants of risk, (*2*) maternal-fetal exposure, and (*3*) current tobacco users. Expert panel consensus regarding current gaps in understanding and recommendations for future research priorities was generated through iterative discussion.

Results: Although much has been accomplished, significant gaps in understanding remain. Implementation often lags well behind insight. This report identifies a number of investigative opportunities for significantly reducing the toll of tobacco use, including: (*1*) the need for novel, nonlinear models of population-based disease control; (*2*) refinement of "real-world" models of clinical intervention in trial design; and (*3*) understanding of mechanisms by which intrauterine smoke exposure may lead to persistent, tobacco-related chronic disease.

Discussion: In the coming era of tobacco research, pooled talent from multiple disciplines will be required to further illuminate the complex social, environmental and biological codeterminants of tobacco dependence.

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Overview

Though it may be difficult to fully appreciate through the lens of our 21st-century understanding, until a relatively short while ago, the impact of tobacco smoke on human health remained a matter of intense debate. Through careful observation and the concerted efforts of scientists from a number of disparate

An Executive Summary of this document is available at http://www.atsjournals.org/doi/suppl/10.1164/rccm.201506-1081ST

Correspondence and requests for reprints should be addressed to Frank T. Leone, M.D., M.S., Comprehensive Smoking Treatment Program, Penn Lung Center, Suite 251 Wright-Saunders Building, 51 N. 39th Street, Philadelphia, PA 19104. E-mail: frank.tleone@uphs.upenn.edu

Am J Respir Crit Care Med Vol 192, Iss 3, pp e22–e41, Aug 1, 2015

DOI: 10.1164/rccm.201506-1081ST
Internet address: www.atsjournals.org

fields, the relationship between tobacco smoke and lung cancer became progressively more clear, leading in turn to important insights about the nature of tobacco-related illnesses and their cures. Today, although we know volumes more about tobacco dependence, it has been difficult to implement a "cure" for this pervasive and tenacious problem.

In an effort to stimulate future concerted research efforts, the American Thoracic Society (ATS) undertook an analysis of the current state of understanding regarding the tobacco epidemic, exploring three areas of special relevance to the global spread of tobacco use and its resulting morbidity. First, understanding what makes a person vulnerable to tobacco dependence, in particular the social, economic, or cultural characteristics that perpetuate tobacco use, can help us improve the specificity of our interventions. Second, understanding the long-term physical and behavioral implications of *in utero* smoke exposure can help us develop a clearer picture of the pathogenesis of chronic illness. Finally, improving our ability to integrate up-to-date treatment information into practice is likely to improve our understanding of the ways in which healthcare systems may augment the effectiveness of ongoing public health interventions.

To this end, this report seeks to summarize the most important scientific observations since the last ATS statement on tobacco was produced, and to place them into the context of ongoing research needs. The report makes several key recommendations, including:

Determinants of Risk

- Despite the empirical success of public policies to reduce the prevalence of tobacco use, significant heterogeneity in implementation limits their effectiveness. Future research should identify the social scientific reasons that population-based policies, known to be effective, are not enacted or enforced. The importance of prevention cannot be overstated.
- Current models of system dynamics in tobacco control suggest nonlinear and interdependent influences on the prevalence of tobacco use. The complex character of the epidemic calls for the development of nontraditional metrics of effect when evaluating proposed population-based interventions.
- Tobacco use prevalence is markedly heterogeneous within the population, with evidence that disadvantaged or minority status may influence use in poorly understood ways. Efforts are warranted to better understand the complex influence of social stigma on individuals' decision making regarding tobacco use.
- Although the impact of social norms on behaviors is clear, our understanding of the methods for facilitating diffusion of new norms remains incomplete. A focused effort to better understand the manner in which cultural shifts are adopted by a population is necessary for facilitating the epidemic's transition through its terminal phases.

The Maternal–Fetal Unit

- Research should continue to focus on the developmental implications of intrauterine smoke exposure, with particular emphasis on the interrelatedness of various disturbances in microenvironment and the importance of exposure timing.
- Interesting epidemiologic associations suggest that the impact of intrauterine exposures may be experienced far beyond the perinatal period. An improved understanding of the mechanisms by which intrauterine smoke exposure may lead to persistent, perhaps heritable, epigenetic changes is of critical importance to the evolving paradigm of tobacco-related chronic disease.
- Future trials of tobacco-dependence treatment during pregnancy should be undertaken with risk–benefit valuations made under assumptions that include the global risks of *in utero* smoke exposure, including those that may be incurred decades after birth.

Current Tobacco Users

- In light of the evolving regulatory environment surrounding healthcare, work should be done to model the manner in which these complex systems experience and react to the interactions between multiple external motivators.
- There is evidence that efficacious healthcare policies may lose effectiveness due to suboptimal implementation strategies. Attention should be paid to understanding the factors that lead to "satisficed," or bare minimum, responses to regulatory system requirements.
- The literature guiding tobacco-dependence training among future healthcare providers remains diffuse. Identifying the most appropriate position for tobacco training curriculum elements within our system of progressive responsibility is necessary to improve self-efficacy as well as alignment between educational methods and clinical skill levels.
- An understanding of the variable nature of nicotine dependence is evolving and is likely to improve our ability to individualize care. Future research efforts that have the potential to more precisely guide treatment decisions, based perhaps on novel biomarkers or other phenotypic characterizations, are warranted.
- The clinical utility of the treatment literature is limited by fidelity to methods that do not clearly reflect the dynamic, adaptive quality of real-world management or the lifelong nature of this chronic illness. Development of nonlinear, stochastic models of disease states, reflecting longitudinal patterns of tobacco use and control over the compulsion to smoke, are warranted.

Introduction

The epidemic of tobacco use in the United States has now been in progress for more than a century. At its peak in the 1960s, the majority of men and more than a third of women smoked cigarettes. There has been a dramatic decrease in the overall prevalence of tobacco use in the United States since the landmark 1964 Surgeon General's Report on Tobacco and Health, declining from 43% in 1965 to about 18% in 2012 (1, 2). However, the decrease in prevalence in the United States

has been uneven and has given rise to stratified epidemics of tobacco use and tobacco-related disease. There are now marked regional differences in tobacco use as well as striking disparities in tobacco use across different segments of the population (1, 3). Given the potency of smoking as a cause of disease and premature death, smoking has become a major contributor to the poor health of many populations in the United States and worldwide.

At the global level, the epidemic of tobacco use is also changing rapidly. Although use has decreased in the United States and other high-income countries, it has increased globally, particularly in low- and middle-income countries. In 2014, most high-income countries were experiencing declining rates of smoking and smoking-related disease, whereas many low- and middle-income countries faced rising smoking rates and the inevitable increase in premature mortality and excess morbidity that follow. Absent marked and immediate changes in current use patterns, the World Health Organization estimates that tobacco use will kill one billion people in the 21st century, with 80% of the deaths occurring in low- and middle-income countries (4).

This truly staggering figure drives the global imperative to forcefully address the tobacco epidemic. On one hand, the World Health Organization's Framework Convention on Tobacco Control (FCTC) has provided a structured policy framework for reducing tobacco use throughout the world (5). On the other hand, there remain significant unexploited opportunities to amplify the impact of global policy initiatives through local action, both in the clinic and the laboratory. In an effort to "think globally while acting locally," the Tobacco Action Committee of the ATS has consolidated the recent advances in tobacco treatment and control into a format accessible to both clinicians and investigators. The project goal was to summarize the available evidence, identify gaps in our understanding, and make recommendations for future research.

Methods

After approval of the project proposal, potential conflicts of interest were disclosed and vetted according to the policies and procedures of the ATS. Committee members worked in three writing groups based on expertise, each charged with assessing the state of current literature within three thematic areas: (*1*) determinants of risk, (*2*) the maternal–fetal unit, and (*3*) current tobacco users. Members searched several databases, including Medline, Embase, and the Cochrane Collaborative, to identify primary sources and reviews. Searches were limited to articles available in English and published since the prior statement of the ATS on tobacco was produced in 1996. Exploded search terms were used to identify the evidence, including terms such as tobacco, addiction, smoking, cigarettes, nicotine, and smoking cessation, in addition to key words unique to each thematic area.

Workgroup members synthesized their evidentiary summaries into a list of candidate topics suitable for inclusion in the final report. An iterative process was used through which the entire committee prioritized and roughly organized candidate topics into a cohesive presentation framework. Each committee member's contribution was edited into an integrated draft, and final approval from the whole committee was obtained prior to publication.

Determinants of Risk

The prevalence of cigarette smoking among U.S. adults remains unacceptably high. Young people continue to experiment and become addicted. There is now a pronounced heterogeneity in tobacco use between members of various demographic groups (1). The basis for this heterogeneity is becoming increasingly well understood. An adaptation of the classic epidemiological triad of host, environment, and agent, linked by the vector, has been used to study these disparities (Figure 1A). When extended to tobacco dependence, the cigarette is the agent, the host is the candidate (or current) smoker, and the environment includes the array of inputs, or determinants, either promoting or opposing the propagation of tobacco dependence within the community. The industry is a true vector, both manufacturing the agent and dynamically

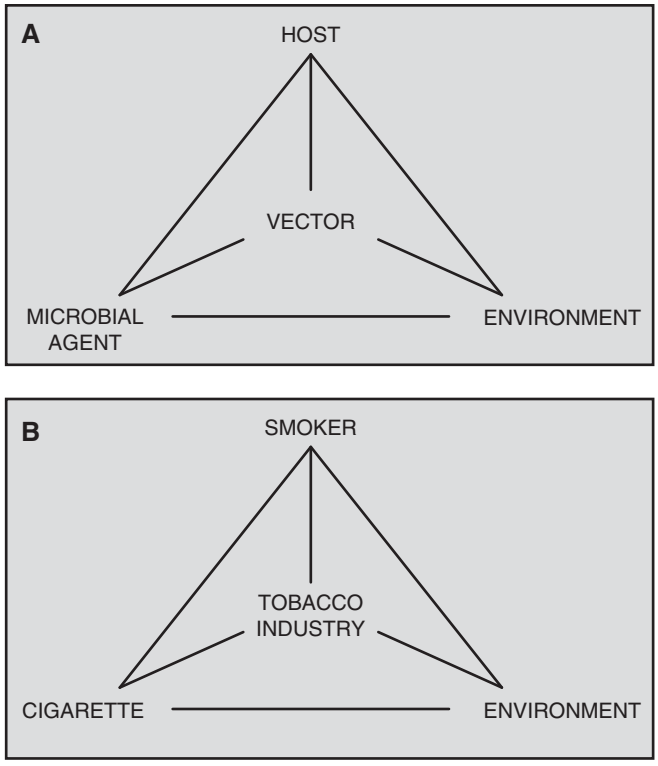

Figure 1. The classic host, agent, vector, environment model of disease transmission (*A*) applied to the tobacco epidemic (*B*).

altering the environment to favor the diffusion of tobacco dependence (Figure 1B). Other, richer models have also been proposed to represent the complexity of interaction between factors that influence smoking prevalence, with the determinants of risk having differential effects based on their prevalence and the degree to which they interact within the environment (1, 6, 7) (Figure 2).

What We Know

Lesbian, gay, bisexual, and transgender community. There has been growing awareness that lesbian, gay, bisexual, and transgender (LGBT) persons constitute communities with distinct healthcare needs (8). An estimated 1.5 to 4.1% of the U.S. population aged 18 to 44 years presently self-identify as homosexual or bisexual. There is an increased prevalence in tobacco use in the LGBT community, with prevalence odds ratios between 1.5 and 2.5 when compared with their heterosexual counterparts (9). The disparity in smoking may be even more pronounced among sexual minority youths. A study by the Centers for Disease Control in nine states and some large urban areas found that current cigarette use ranges from 8 to 19% in heterosexual students, but 20 to 48% in gay and lesbian students (10). Culturally tailored smoking cessation programs have been shown to be effective in the LGBT population (11).

People with mental illness. It is estimated that 19.9% of adults in the United States 18 years or older, or 44 million people, have a mental illness (12). People with serious mental illness die 25 years prematurely, and prominent among their reported causes of death are tobacco-related heart disease, cancers, and lung disease. The prevalence of smoking among people with mental illness is 36.1%, nearly twice that of the general population (13). People with mental illness also smoke more cigarettes, accounting for an estimated 30.9% of sales in the United States. Interestingly, sociodemographic variation in smoking among people with a mental illness parallels that of the general population.

Although smoking contributes heavily to morbidity and mortality among the severely mentally ill, the effectiveness of cessation interventions in this group remains a matter of ongoing investigation. As a general rule, treatments that work in the overall population appear to also work in patients with severe mental illness. The magnitude of the anticipated treatment effect has been variously reported, with some estimates suggesting approximately equal effectiveness compared with the general population and others suggesting lower cessation rates in this group (14, 15). Treating tobacco dependence in patients with stable psychiatric conditions does not worsen control of their mental health (16, 17) and appears to be associated with a modest reduction in risk for mood/anxiety disorders (18, 19).

People who are incarcerated. Nearly 2.3 million adults were incarcerated in the United States in 2010 (20). Smoking rates are three to four times higher among prisoners than in the general population, with estimates as high as 80% among adult prisoners and 46% among those in juvenile detention facilities (21). Correctional facilities have established restrictions on smoking over the past 20 years, but these measures have not reduced smoking prevalence. Although programs and materials to assist with smoking cessation are generally unavailable in prisons, research has shown that treatment of tobacco dependence with behavioral counseling and nicotine replacement therapy is equally effective in women who are incarcerated as in the general population (22).

Low-income and low-education populations. According to the U.S. Census Bureau, 15% of the population, or 46.5 million people, lived below the federal poverty level in 2012 (23). The prevalence of current smoking is significantly higher among adults living below the federal poverty level than among those at or above this level (24). Among homeless adults, the prevalence is approximately 75%, perhaps in part reflecting the high prevalence of serious mental illness in this group (25). Smoking prevalence also varies greatly by educational level, highest among adults who have obtained a General Education Development certificate (49.1%) and lowest among adults with a graduate degree (5.6%) (24).

Native American populations. American Indian and Alaska Native (AI/AN) populations have a higher prevalence of current smoking than most other racial and ethnic groups in the United States, although there is substantial variation among tribal groups (24). In 2011, 31.5% of AI/AN adults smoked, compared with 19.0% of all U.S. adults, higher among AI/AN men (34.4%) than among AI/AN women (29.1%).

Military veterans. Cigarette smoking has been recognized as a significant problem among both active members of the Armed Forces and veterans (26). The overall age-adjusted prevalence figures between 2003 and 2007 were 27% for veterans and 21% for nonveterans. Differences were even more striking when stratified by age. The highest prevalence was observed among the youngest veterans, with 37% of those born between 1985 and 1989 and 36% of those born between 1975 and 1984 smoking cigarettes.

Adolescents. Within several developed economies, recent estimates of adolescent tobacco use prevalence suggest an encouraging, continued decline, whereas progress made within developing economies remains less clear (27–30). Although a majority of effort has traditionally been dedicated to efforts to prevent initiation among young people, it is clear that many teenage smokers would like to quit and begin experiencing dependence symptoms within a short time of starting (31). Several behavioral modification approaches show promise, including those incorporating motivational enhancement methods and cognitive behavioral therapy (32). Pharmacologic interventions have been relatively disappointing, especially when compared with their impact on adult counterparts.

Impact of tobacco industry practices. Aggressive integrated marketing and promotion by the tobacco industry, and images of smoking in the media, are major drivers of experimentation and initiation, as well as continued smoking (1, 6). Ten billion dollars per year—more than a million dollars per hour—are spent on tobacco marketing in the United States alone (1). A 2011 Cochrane review of 19 longitudinal studies, involving more than 29,000 individuals aged 18 years or younger who did not smoke regularly at baseline, found that tobacco advertising

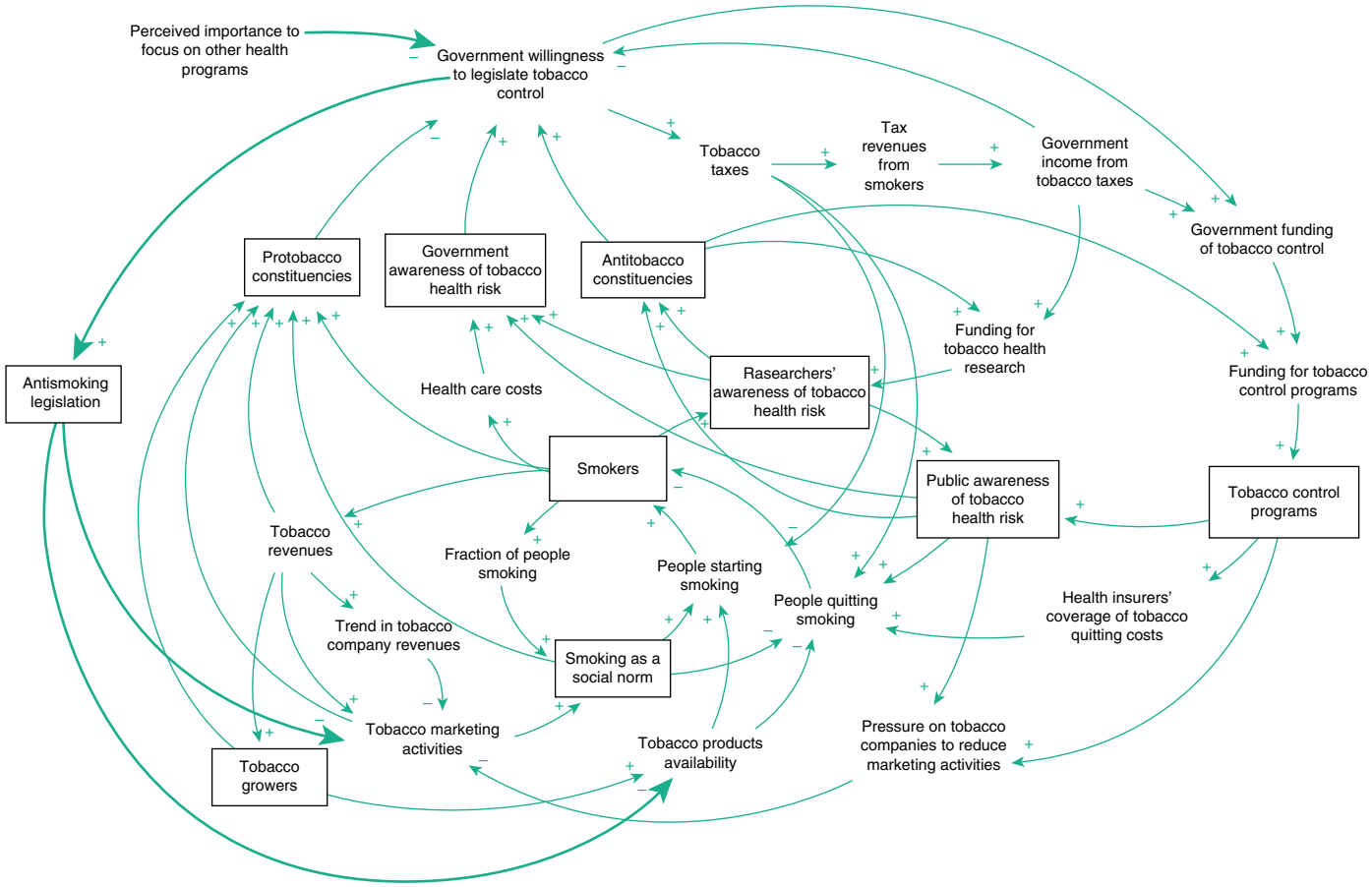

Figure 2. System dynamics model for tobacco control illustrating the nonlinearity and complex interdependence of variables influencing the prevalence of tobacco use (adapted from Reference 84).

and promotion increase the likelihood that adolescents will start to smoke (33). In a cohort study of German youths aged 10 to 15 years who were never-smokers at baseline, the highest tertile of exposure was associated with a doubling of daily and established smoking rates compared with the lowest. Every 10 tobacco advertising contacts with a young person increased the adjusted relative risk for established smoking (>100 cigarettes ever) by 38% and by 30% for daily smoking. There was no association with nontobacco advertising contact, indicating that exposure to tobacco advertising was not simply a marker for overall advertising exposure (34).

Point-of-sale advertising, cigarette displays, flavored small cigars, and retail promotions are currently less tightly regulated than other types of tobacco advertising and consequently emphasized by the industry (35). Young adults aged 18 to 24 years are twice as likely as older adults to make unplanned cigarette purchases in response to point-of-sale advertising (36, 37). There is a higher density of point-of-sale advertising in stores where youth frequently shop, including those close to schools and in low socioeconomic areas (38, 39). Targeted advertising to African Americans has been identified within tobacco industry documents, especially for menthol brands, with disproportionate exposure to outdoor and point-of-sale advertisements. African American students aged 11 to 15 years were three times more likely than other students to recognize the Newport brand and less likely to recognize Marlboro. Regardless of race, recognition of Newport cigarette advertising at baseline was associated with higher rates of smoking initiation within 12 months (40).

Perhaps most importantly, the Internet and social networking sites provide new, substantial, and inexpensive venues for tobacco advertisements and tailored imagery (41–43). Because cost is an important factor influencing tobacco use by youth, a majority of marketing dollars are used to lower the cost of cigarettes to consumers, particularly with price-reducing promotions and coupons (6, 36).

Tobacco imagery in film plays an important and well-established role in smoking initiation. The history of the industry's efforts to place smoking within movies is well documented (44). Acknowledging substantial evidence from cross-sectional, longitudinal, and experimental studies, the U.S. Surgeon General's 2012 report stated that "The evidence is sufficient to conclude that there is a causal relationship between depictions of smoking in the movies and the initiation of smoking among young people" (6, 7). Children 10 to 14 years old within the highest quartile of exposure were found to be 2.6 times more likely to initiate smoking as those in the lowest quartile (45). In a study conducted across six European countries, the estimated mean exposure to on-screen tobacco was 1,640 occurrences, with each 1,000

increasing the adjusted relative risk for smoking onset by 13% (46). An estimated 37 to 44% of adolescent smoking initiation has been attributed to exposure to smoking in movies, roughly 800,000 adolescents aged 12 to 17 years in 2012 alone (47). Despite the ban on paid placement of tobacco products imposed by the 1998 Master Settlement Agreement, and resolutions by the National Association of Attorneys General calling for a reduction of tobacco depictions in feature films, smoking in youth-rated films increased 38% from 2013 to 2014, resulting in 10.8 billion tobacco impressions (paid admissions × tobacco incidents) (48, 49). The number of viewed incidents increases exponentially when international markets and other film venues are considered.

Personal relevance may moderate the impact of tobacco use depictions on smoking initiation (50). African American youth see more tobacco use in mainstream media than do white youth but are less responsive to it, unless it is connected with African American–oriented themes or characters (51, 52). Among Mexican-born youth, exposure to smoking imagery in movies is a strong independent predictor of initiation, more so than for U.S.-born Mexican American youth, possibly related to the acculturation process (53). Media have been shown to be more influential among adolescents at low to moderate risk for smoking rather than at either extreme (52).

The vulnerability of youth. Smoking initiation is generally defined as the first instance of cigarette smoking, ranging from a single puff to an entire cigarette. In the United States, almost 90% of those who move on to smoking regularly have their initial experience with smoking before age 18 years and another 10% by 25 years (1). During the transition period to adulthood, before psychosocial skills are fully mature and while the brain is most developmentally plastic, a young person's limitations in consequential thinking and decision making can be associated with impulsivity and risk taking. The confluence of youthful experimentation and neuronal susceptibility to the trophic effects of nicotine increases adolescents' risk of developing lifelong addiction. The tobacco industry has long taken advantage of this window of vulnerability through its marketing strategies (6). The most susceptible 10% lose autonomy over tobacco use within 2 days of first inhaling, and 50% of those who develop dependence do so by the time they are smoking two cigarettes a day (54). In 2012, the prevalence of current cigarette use among middle and high school students in the United States was 3.5 and 14.0%, respectively, whereas the prevalence of current tobacco use was 6.7 and 23.3%, respectively (55). Noncigarette tobacco products, such as candy-flavored cigars and electronic cigarettes (e-cigarettes), often cost less and are increasingly popular, raising concerns that they may lead to cigarette smoking. Although these products are not yet regulated by the U.S. Food and Drug Administration (FDA), the agency recently issued a proposed rule extending its regulatory authority to include alternative tobacco products not already under the authority of the FDA (i.e., e-cigarettes, cigars, pipe tobacco, nicotine gels, hookah tobacco, and dissolvables) (56).

Social determinants of health. Several important social determinants of health are also believed to influence tobacco use and are commonly encountered among underrepresented minority populations. The importance of stigma—the labeling, stereotyping, separation, status loss and discrimination that occurs within a context in which power is exercised—is increasingly recognized. It is pervasive, negatively impacts social relationships and coping mechanisms and has been associated with increased rates of smoking (57). Social stressors, such as low socioeconomic status, unemployment, and lack of health insurance, cross racial, ethnic, and geographic lines. The 2000 Surgeon General's Report noted the impact of the "tobacco industry's practice of targeting cultural and ethnic minorities through product development, packaging, pricing, advertising and promotional activities" as a marketing strategy that provides validation to marginalized individuals and communities (58).

Lesbian women and gay men smoke cigarettes at nearly twice the rate of their heterosexual counterparts (1, 59). Bisexual and transgender people may smoke at even higher rates, but data are limited. Sexual minority youths start smoking at younger ages, and young lesbian women smoke more cigarettes per day and have higher levels of nicotine dependence than heterosexual women (60). Proposed reasons for the disparities include higher rates of stigmatization, discrimination, stress, social rejection and lack of support, childhood adversity (including being bullied), violence victimization, depression, internalized homophobia, targeted marketing by the tobacco industry, and unequal access to healthcare (57, 59, 61–63). LGBT youth encounter various levels of acceptance within their families and communities and experience high rates of homelessness (64). There is no available evidence or theoretical framework that suggests sexual orientation/identity in itself causes tobacco-related disparities (59).

As confirmed by internal documents, the tobacco industry has engaged in targeted marketing of sexual minorities since the 1990s, with campaigns including Project SCUM (Sub-Culture Urban Marketing), advertising in LGBT magazines, sponsoring LGBT activities, and providing free cigarettes in LGBT venues (65). Sexual minorities have been seldom reflected in mainstream media, and the social acknowledgment, validation, and legitimization provided through marketing have been powerful tools, seen by some LGBT people as a benefit that more than offsets tobacco's ill-health effects (65–67). Ads emphasize liberation, pride, individualism, social success and acceptance. LGBT publications have had fewer funding/advertising sources than mainstream media and have relied more on the tobacco industry for support. Publications containing tobacco advertising are less likely to include information on the health risks of tobacco and contain more images of people smoking in general. Sexual minorities are often unaware of disproportionate smoking rates or of targeting by the tobacco industry (47).

More than nine million adults (2–3%) in the United States self-identify as LGBT (59). Improving the health of lesbian, gay, and bisexual individuals is a goal of Healthy People 2020, yet the Institute of Medicine has highlighted the paucity of guiding data, especially for bisexual and transgender populations (68). Rates at which people refuse to answer questions on sexual orientation and gender identity are low. Yet, only 12 states have included such questions in their Behavioral Risk Factor Surveillance System surveys. No

states in the U.S. South, where smoking rates are higher than in other parts of the United States, include these items (59). The omission of sexual orientation and gender identity questions in most U.S. state and federal health surveillance programs, especially for youth, has impeded efforts to determine and eliminate disparities.

Variation in nicotine's addictive potential. Nicotine is delivered in the tobacco smoke aerosol at a high concentration. Recent work suggests that variations in nicotinic cholinergic receptors influence the addictive liability of nicotine (1, 69). The extent to which genetic and other biologic factors contribute to observed subpopulation disparities remains under investigation. Exposure to nicotine leads to tolerance, driven by a variety of functional changes within the brain (69–71). Patients experience a wide variety of withdrawal symptoms and display significant variability in addictive behaviors as a result (72).

Novel approaches to tobacco control. Because initiation occurs during adolescence for most people, preferred media for social networking may be effective for promoting abstinence from smoking. The landmark National Cancer Institute report on the role of mass media in controlling tobacco use suggests that exposures eliciting a strong adverse negative response to smoking reduce smoking initiation and alter young people's attitudes toward smoking (7). Whether the interpersonal connections and group affiliations reinforced by social media impact can also influence quit decision making remains unclear. Exposure to Internet tobacco advertising and promotion is associated with an adolescent's decision to initiate smoking (33). The evidence is strengthened by an apparent dose–response and temporal relationship and consistency of effect across multiple observational studies (7, 73–75).

Images typically depicting either adverse health consequences of cigarette smoking, such as lung cancer, tracheotomy, and cachexia, or surrealistic portrayals of offensive aspects of smoking, such as a gravid abdomen with a cigarette protruding from the umbilicus, have been placed at point-of-sale sites. Positive results, including increased awareness of health risks and increased thoughts of quitting, have been reported (76).

Pictorial warnings on cigarette packages have been advocated as a strategy to increase the motivation to quit among active smokers (77). In 2005, the World Health Organization mandated health warnings on tobacco packages sold in countries that ratified the FCTC (78). Such warnings should cover at least 30% of the package surface area and be "large, clear, visible, and legible." Although the United States did not ratify the FCTC, the FDA did require that colored graphic warnings cover 50% of the front and back of each cigarette package sold and 20% of cigarette advertisements displayed in the United States, under authority of the Family Smoking Prevention and Tobacco Control Act. This policy was consistent with those previously implemented in Canada, Australia, Brazil, and Thailand. A 2011 legal challenge by five tobacco manufacturers, partially upheld on appeal, was decided in favor of the tobacco companies because the government's graphic warning requirements lacked a sufficient evidentiary basis (79). Australia, on the other hand, has implemented policies requiring cigarette companies to use uniform plain packaging, without any obvious brand signatures, because brand identification contributes to initiation and maintenance of smoking behaviors (80). Pilot studies suggest a reduction in smoking interest and a heightened awareness of negative health implications among youth exposed to such packaging (81).

What We Need to Know

There is growing evidence that some individuals are more susceptible to the harmful effects of tobacco than others, either because of cooccurring genetic or environmental risks or because of underlying comorbid conditions. In the future, we may be able to characterize the at-risk groups more fully using genetic approaches. The changing face of the tobacco epidemic, from one affecting the population as a whole to one that especially affects specific segments of the population, is a major contributor to health inequality in the United States and other high-income countries. The contribution of smoking to health disparities warrants further study and should motivate a reexamination of relevant public health strategies.

The 2000 Surgeon General's report advised that economic, regulatory, and comprehensive approaches will have the greatest population impact on tobacco use (58). Protective interventions such as counter-advertising, increasing the price of tobacco products, and global bans on all forms of advertising, promotion, and sponsorship, would go far in reducing smoking initiation (1, 4, 6, 36, 82). Gaps remaining include an understanding of how health system interventions might be brought to bear to more effectively contribute to reductions in initiation and maintenance rates, alongside improvements in cessation rates. Ample insights are available to guide a substantial decrease in the number of people who start smoking, yet very few effective policies have been broadly enacted. Important areas for future research should include determining the social scientific reasons that such policies are not already in place and/or enforced, including identifying barriers to remedying a global political environment permissive of ongoing tobacco industry efforts to addict young people to nicotine.

Research opportunities for augmenting ongoing tobacco control efforts must account for the special nature of the relationship between the multiple "players" acting across various levels of societal organization (Figure 2). This underlying complexity may call for investigation of nonlinear responses to the epidemic, using novel or nontraditional metrics of effect. For example, a deeper understanding of the ways in which widely disseminated prevention messages may adversely impact the stigma experienced by disparate populations, and later affect their rates of engagement with medical treatment for tobacco dependence, may inform a strategic approach to capitalize on the complex interplay between the biological, social, and environmental determinants of smoking.

The system inputs that influence tobacco use are dynamic and interactive and are not necessarily linear. These chaotic relationships raise the possibility that policies may result in consequences not anticipated under linear assumptions. This type of nonlinear behavior change was popularized by Gladwell in *The Tipping Point* (83) and was the topic of the National Cancer Institute's Monograph 18, *Greater than the Sum* (84). Robust

relational models should become the basis for computational representations of the mechanisms by which individuals within a population cross important "state thresholds" and should inform more stochastic, nonlinear models of state transitions within populations.

The 1964 report of the Advisory Committee to the Surgeon General identified smoking as a cause of lung cancer and other diseases as well as increased all-cause mortality (85). The inference of causation was based on the strength of the accumulated evidence and motivated widespread public action. Similarly, the 1986 determination that involuntary smoking caused lung cancer in never smokers motivated indoor smoking bans and other measures (86). We do not yet adequately understand the manner in which these shifts in thinking were culturally adopted or the manner in which they impacted the population's transitions through important threshold states. A better model would be valuable in accelerating successes while avoiding failures. Future tobacco control research priorities could be targeted strategically, potentially designed to move populations toward a target threshold rather than using single linear outcome.

Maternal Tobacco Exposures during Pregnancy

A pregnant woman who smokes, smokes for two. Maternal smoking during pregnancy results in fetal exposure to tobacco smoke constituents 20 times higher than from exposure to secondhand smoke later in life and is likely to have lifelong consequences for the child (87). Fetal smoke exposure can lead to premature birth (88), low birth weight (87, 89), and a variety of birth defects (90). It appears to double the risk for sudden infant death syndrome, possibly by increasing the inner wall thickness of lower airways (91, 92).

The effects of maternal tobacco exposure during pregnancy may be difficult to discriminate from the impact of secondhand smoke exposure during infancy and early childhood, as smoking during pregnancy frequently continues afterward. Interestingly, studies support the notion that *in utero* smoke exposure may have an important impact on lung function during childhood, as does secondhand smoke exposure after birth (93).

What We Know

Consequences for the child. Measurements of lung function within 2 to 5 days of birth suggest a dose-dependent reduction in both tidal breathing, as estimated by the ratio of time to reach peak tidal expiratory flow to the total expiratory time, and passive respiratory mechanics, such as respiratory system compliance (94, 95). Studies of lung function measured later in life also suggested that smoking during pregnancy had a substantial detrimental and long-lasting effect (93). This pattern suggests that there is a window of susceptibility during pregnancy, within which the influence of maternal smoking on the fetus/child's lung development both *in utero* and later in life is greatest, supporting the hypothesis of an early origin of risk for adult respiratory disease.

There appear to be several mechanisms through which maternal smoking during pregnancy affects lung function in the newborn and later. Postmortem studies of victims of sudden infant death syndrome have found significantly increased inner airway wall thickness, with collagen deposition and alveolar tethering, among the children of smoking mothers compared with similar children of nonsmoking mothers (92). In animal models of fetal lung development, *in utero* exposure to nicotine increased pulmonary expression of the α-7 nicotinic acetylcholine receptors, resulting in impaired alveolar development, altered branching morphogenesis, and altered newborn pulmonary function (96–100). Analogous human epidemiologic findings include observations that *in utero* tobacco smoke exposure appeared to synergistically affect the decline in lung function experienced by children with early-onset asthma. The absolute differences in forced expiratory flow in the midexpiratory phase associated with *in utero* smoke exposure increased with age among children diagnosed with early-onset asthma, although little evidence of an effect of secondhand exposure alone was identified when the children were followed until 8 years of age (101).

Single nucleotide polymorphisms of the β_2-adrenergic receptor gene appear to interact with exposure to maternal smoking to influence respiratory outcomes. Children homozygous for the Arg16 allele who were also exposed to smoke *in utero* had a threefold increase of lifetime wheeze, suggesting important early developmental environment–gene interactions may reduce lung function long term (102). Fetal smoke exposure has also been found to relate to several epigenetic changes, including increased DNA methylation of the AXL tyrosine kinase receptor, relevant to immune function and the development of allergic disease (103). These subtle but important changes appear to persist for years after birth. DNA methylation of blood mononuclear cells was found to be statistically significantly associated with a history of maternal smoking during pregnancy among adult women in their fifth decade of life within a New York City birth cohort (104). Changes in DNA methylation resulting from *in utero* smoke exposure may represent one plausible mechanism by which early exposure affects risk of illness much later in life. The possibility that these epigenetic risk factors for respiratory illness could be inherited through generations has been proposed (105).

Smokeless tobacco products and electronic nicotine delivery systems (e-cigarettes) are presently being heavily marketed around the world. Oral tobacco products such as snuff have increased in use among adolescents in the United States and Scandinavia, although they are forbidden within the European Union. The increased use of these alternative products among adolescents and women of childbearing age is a growing concern, in part because substitution of these products in place of cigarettes and in lieu of abstinence may in fact cause an increase in *in utero* exposure to nicotinic products. There is a paucity of direct data about the intrauterine delivery of nicotine from snuff or e-cigarettes or the effects of their use on the developing fetus. Moist snuff, also known as snus, has been associated with an increased risk of spontaneous preterm birth, particularly before 32 weeks' gestation, suggesting a significant fetal exposure (106).

Consequences for the mother. Maternal smoking during pregnancy is associated with a number of important demographic covariates, including

younger age, lower socioeconomic status, and lower education levels. Compared with women in their respective reference groups, women who smoke during pregnancy are also more likely to have a greater number of children, an active history of drug or alcohol use, substandard prenatal care, an absent partner, or a partner who smokes (107–109). Age at pregnancy has a significant influence on the observed racial/ethnic disparities in antepartum smoking, with prevalence in younger non-Hispanic whites (46.4%), Alaska Natives (55.6%), and American Indians (46.9%) considerably higher than observed in their older counterparts (110).

Pregnant women who smoke are at risk of ectopic pregnancies, spontaneous abortions, placental abruption, placenta previa, and other pregnancy complications (108, 111, 112). Ectopic pregnancies account for approximately 10% of maternal deaths in the United States (113). Pelvic inflammatory disease is an important risk factor for ectopic pregnancies. Cigarette smoking appears to be an independent risk factor for ectopic pregnancy as well as a risk factor for pelvic inflammatory disease (113, 114).

Spontaneous abortions associated with cigarette smoking may be due to the toxic effect of nicotine, carbon monoxide, and other constituents of tobacco smoke (112). Although many studies have found an association, the strength of the association is modest (112). The estimated relative risk ranges from 1.0 to 1.8, and only a few studies have found a significant dose–response relationship (114, 115). Placental abruption, with a prevalence ranging from 0.4 to 2.0% in the United States, is more strongly associated with cigarette smoking (114). A Canadian study found that women who smoked during pregnancy had a relative risk of placental abruption of 2.05 (95% confidence interval, 1.75–2.40) compared with nonsmokers, independent of parity (116). Multiple mechanisms may be involved, but it is believed that the decreased levels of ascorbic acid in smokers, important for collagen synthesis, may predispose maternal smokers to ruptured membranes and early separation of placenta from the uterine wall (115, 117).

It has been postulated that the association between placenta previa and cigarette smoking may relate to increased levels of carbon monoxide in maternal blood and a relatively hypoxemic microenvironment that results in placental enlargement (115). The reported magnitude of the association varies, with relative risks of 1.5 to 3.0 (114, 116). Women whose pregnancies are complicated by placenta previa are also at increased risk of severe vaginal bleeding, both antepartum and during delivery (112, 114, 118).

On a molecular level, women who smoke during pregnancy increase their risk of oxidative DNA damage (119). Oxidation damage is an important mechanism of carcinogenesis, and the metabolites produced can be transferred to the fetus (119). Smoking enhances lipid peroxidation and depletes the antioxidant potential of β-carotene, vitamin A, vitamin E, and uric acid in both the plasma of pregnant women and umbilical cord blood, perhaps resulting in free radical damage to both the mother and the growing fetus (120). Smoking also increases plasma lead concentrations in the mother, with a negative effect on the transplacental flow of micronutrients and an adverse influence on both intrauterine and childhood development (121). Plasma lead levels correlate with the intensity of cigarette smoking among the pregnant women studied and may be a result of mobilization of calcium from the bone with simultaneous release of lead deposited in the bone. Metabolism of developing bone may also be affected by an associated increase in parathyroid hormone and alkaline phosphatase (122).

Cigarette smoking has a negative influence on breast milk volume after birth, with nonsmoking mothers producing more than 30% more breast milk than smoking mothers (mean, 961 ml/d vs. 693 ml/d, respectively) (123). A lower infant growth rate among the children of smoking mothers has been hypothetically connected to this difference, with breast milk volumes perhaps insufficient to support the energy requirements of the infants (123). A number of cytokines typically found in human breast milk were not present in the milk of smoking mothers, leading some to hypothesize a mechanistic relationship to the observed increase in the newborns' susceptibility to infections (124).

More than 50% of smoking women do not quit smoking during pregnancy (125). Those who quit do so primarily out of concerns over fetal and infant health and typically begin abstinence early in pregnancy (112, 114, 118). Given the multiple prenatal visits to a healthcare professional, pregnancy may be a teachable moment and an ideal time for smoking cessation interventions. A Cochrane review of 72 trials of approaches to treatment of tobacco dependence in this population suggested that the most common interventions were based on cognitive behavioral therapy, followed by transtheoretical model of change, feedback, incentives, and pharmacotherapy (126). The authors concluded that these types of interventions are effective in promoting maternal cessation and reducing preterm and low-birth-weight births, with an increase in mean birth weight of 53.91 g. However, there appeared to be no statistically significant differences in neonatal intensive care unit admissions, very low birth weight, stillbirths, or perinatal or neonatal mortality.

What We Need to Know

It is becoming increasingly clear that the impact of maternal tobacco exposure on fetal development extends well beyond acute concerns such as placental blood flow and fetal cardiovascular tone. The introduction of smoke and its constituents into the maternal–fetal relationship fundamentally alters the environment within which the processes of development take place and demands an adaptive response that has implications during early life, adulthood, and conceivably for subsequent generations. Research should continue to focus on the developmental implications of intrauterine smoke exposure, with particular emphasis on the interrelatedness of disturbances in microenvironment and the impact of timing of exposure. Although it seems there may be particularly vulnerable periods during development, the interactions between the timing of exposure, the sequence of downstream biological effects, and the development of serious and/or lifelong consequences remain unclear. One particularly promising model shedding light on the complex relationship between *in utero* smoke exposure and subsequent illness is highlighted in our understanding of lung

development and lung function decline. What are the implications on how we think about the origins of adult respiratory diseases like chronic obstructive pulmonary disease?

There is increasing evidence that intrauterine smoke exposure leads to persistent, perhaps heritable, epigenetic changes. Although most women who stop smoking during pregnancy do so out of concern for their developing baby, it remains unclear whether the influence of tobacco smoke exposure extends farther back, even before pregnancy, or whether a cumulative generational effect may impact risk within families of maternal smokers. Analogously, the relative short- and long-term impact of exposure to smokeless forms of tobacco products on the fetus, including the health implications of the emerging e-cigarette, remain to be identified.

Longitudinal studies are needed to assess the cumulative impact of smoking and oxidative damage. Evolving genomic and proteomic techniques should be brought to bear to understand the mechanisms through which mother and child share the impact of smoking. These techniques may help us to understand the early origins of adult respiratory disease.

Data on the interplay between multiparity and smoke exposure are currently lacking. Are multiparous smokers at increased risk of comorbidities, healthcare use, and mortality during and after pregnancy? Does this differential risk contribute to observed subgroup disparities in health outcomes?

Although investigating the basis of pathogenesis is important, more can be done to develop better integrated and collaborative approaches to controlling tobacco dependence within this critical subpopulation of smokers. Pragmatism has required that pharmacotherapeutic clinical trials exclude pregnant women from enrollment. This trend has recently changed, and the forward-looking focus on trials of pharmacotherapies during pregnancy is encouraging (127). Future trials should be undertaken with risk–benefit valuations made under assumptions that include the global risks of *in utero* smoke exposure, including those that may be incurred decades after birth. We need to further explore and describe the biological, social, and cultural factors that influence smoking behavior during this critical time and use this insight to develop novel approaches to improving cessation rates among pregnant women.

Caring for Current Smokers

Despite the availability of well-developed clinical practice guidelines, fewer U.S. healthcare providers are offering tobacco-dependence counseling today than a decade ago (128, 129). The proportions of practitioners who provided counseling in 2000 and 2005 were 53.3 and 58.9% respectively, but declined to 50% in 2010. Data from the U.S. National Ambulatory Medical Care Survey suggested that tobacco-dependent patients were less likely to receive treatment for their condition than patients with other chronic conditions (130). The overwhelming health impact of tobacco use coupled with the evidence suggesting that healthcare providers can positively influence their patients' ability to quit imply a stark need for meaningful tobacco treatment education. Clinicians with the knowledge base and demonstrated ability to implement evidenced-based strategies may facilitate a decrease in smoking rates, reduce the rates of tobacco-related illnesses, and lower the costs associated with treating these comorbid conditions.

Smokers who receive advice from a healthcare professional about cessation are more likely to make a quit attempt than those who do not (131). In addition, smokers whose primary care physicians counseled them about their tobacco use reported increased satisfaction with their care, in degrees directly proportional to the number of counseling interventions received (132). Although some individuals are able to quit smoking without assistance, the combination of counseling and medications more than doubles quit success (128). Tobacco treatment support systems have been embedded into electronic health records and have successfully augmented provider efforts to screen patients for tobacco use at every encounter (133).

What We Know

Barriers to patient engagement in tobacco-dependence treatment. Tobacco users perceive obstacles to quitting and consequently are less apt to make quit attempts or consult their healthcare provider for assistance. Internationally, a number of studies have identified several important barriers to quitting, including patients' self-doubt regarding their ability to quit, concern over loss of their stress reliever, fear of weight gain, lack of knowledge related to available support, the high cost of nicotine replacement therapy, and anticipated continuing exposure to tobacco use through personal relationships (134, 135). Some identified obstacles to cessation attempts can be directly influenced by clinicians, including patients' concerns over the safety and effectiveness of nicotine replacement therapy and their concerns about being unfairly judged by healthcare providers, policy makers, and those who do not use tobacco (136, 137).

The impact and significance of these barriers appear to vary between demographic groups. In a survey of nearly 8,000 U.S. adults, women were more likely than men to report loss of their preferred stress-relief method, concerns about cravings, and the potential for weight gain as their most important perceived barriers to quitting (138). Younger smokers were more likely to express concern about disruption in social relationships than older counterparts. Concerns over cravings and withdrawal symptoms were associated with heavier rates of smoking. Similar concerns persist, whether the counseling is delivered in person or by telephone (139).

Barriers to clinician engagement in tobacco-dependence treatment. Physicians in 16 countries were interviewed to determine their smoking status, attitudes toward smoking, and practice regarding tobacco-dependence treatment (140). Physicians who smoked were less likely to discuss tobacco use at every visit and believed that patient barriers were related to a lack of willpower or interest. Nonsmoking physicians were more likely to view smoking as a harmful activity and quitting as the single most important step to improve health. Nonsmokers were also more likely to use a systematic approach to delivering tobacco-dependence treatment, including counseling and medication recommendations. In a study of Chinese physicians, "gifting" of cigarettes to doctors was reported as an additional

barrier to providing tobacco-dependence treatment (141).

The impact of life experience on clinician decision making is not limited to physicians. A national study surveying several types of practitioners in the United States confirmed that nonphysician providers were also significantly less likely to offer tobacco-dependence treatment if they were current smokers (142). Other barriers to treatment included feeling discomfort when asking about tobacco use, holding the opinion that counseling was not an appropriate service for them to provide, dealing with competing priorities, and believing that patients would resist advice. General practitioners cite limited time, insufficient training, and lack of reimbursement for counseling, in addition to their self-perceived lack of knowledge and skill in dealing effectively with tobacco-dependent patients (143).

The distinction between smoking cessation and treatment of tobacco dependence. The implications of the language we have adopted to describe the change in status from tobacco user to nonuser are not subtle. Inherent in the terms are explicit assignments of responsibility. The noun "cessation" refers exclusively to the tobacco user, whereas the noun "treatment" refers to the joint responsibilities of both patient and clinician. Word choices provide important clues to the cultural assumptions and presuppositions that may be affecting our approach to the problem.

It is clear that beliefs regarding illness causation, and subsequent inferences about culpability in the matter, profoundly influence the willingness to invest effort in giving help (144). In the "sin-versus-sickness" framework of social motivation, the notion of causal controllability is defined as the capacity of individuals to volitionally alter the causes of illness. Impressions of causal controllability are often instinctive and need not align with rational or expressed understanding. Perceived failures are often accompanied by an instinctive attribution of causality. If the failure is attributed to environmental or social causes, judgments that follow are generally accompanied by emotions of pity or sympathy. If, however, attribution is to the individual's constitutional traits, judgment is often accompanied by anger or frustration. The degree to which instinctive impressions of causal controllability affect caregiver behaviors depends on whether the patient is perceived as participating in their cure as well as the extent to which they resemble or are familiar to us (i.e., the degree to which we can empathize with their position) (145). Observations of providers' approach to individuals with stigmatized condition, such as AIDS, drug addiction, and obesity, suggest that the implications of causal controllability are resolvable, requiring first recognition of the effect followed by a conscious refutation of the emotional consequences (144, 146, 147).

Tobacco dependence as a chronic illness. Nicotine is a naturally occurring alkaloid that binds to nicotinic cholinergic receptors in the brain, leading to the development of dependence (69). The nicotine in cigarette smoke is suspended in both the particulate and gaseous phases of the aerosol. The addition of several compounds, including ammonia, to the tobacco leaf during production increases the fraction of nicotine in the freebase form (148, 149). Because freebase nicotine is more readily volatilized, it can be deposited across the large surface area of the airways and alveoli. Pharmacokinetics of central nervous system (CNS) delivery depend heavily on the proportion of nicotine elaborated in freebase form when the tobacco is heated (150, 151). The nicotine in a puff of smoke reaches the brain as quickly as 10 seconds after inhalation, giving the smoker an immediate dose and producing relief of craving (152).

The neurophysiologic consequences of sustained nicotine exposure are protean (69). Nicotinic acetylcholine receptors are located in all areas of the mammalian brain, but the main effectors of addiction are particularly concentrated in the mesolimbic dopaminergic system and the locus ceruleus (153). These sites are of critical importance to basic survival functions of the organism. The mesolimbic dopaminergic system plays a central role in orchestrating survival behaviors by activating an instinctual "appetitive" state, motivating goal-directed behaviors and influencing the cognitive processes necessary for overcoming barriers to gratification of the instinct (154). Because nicotine has the ability to act as an exogenous ligand, it reliably activates endogenous cholinergic receptors in the survival centers of the brain, creating a powerful but artificial safety signal. Its ability to hijack fundamental survival systems makes nicotine one of the most potent neuropharmacologic drugs of abuse, more capable of compelling behavior than "classic" drugs of abuse, including cocaine, amphetamine, and morphine (155). In the clinic, tobacco dependence is manifest in patients' instinctive compulsion to smoke despite rational reasons not to.

Dependence results from the interaction between a defined biochemistry and the physical determinants of disease, in a manner similar to that of other chronic medical conditions (128, 156). Demonstrable behaviors have been associated with alterations in CNS structure and function (70, 157). For example, specific single nucleotide polymorphisms have been associated with the predisposition to smoking initiation, maintenance patterns of cigarette use, and the ability to stop using tobacco (158). Biological variations in the susceptibility to nicotine dependence is amplified by the fact that the onset of regular cigarette use typically occurs during adolescence, a time when the brain is in a state of high plasticity (6).

Within about 10 days of daily cigarette use, the $\alpha_4\beta_2$ nicotinic acetylcholine receptors in the CNS have desensitized (159), and their density has increased two- to threefold (160–166). Nicotine increases the tone of several neurotransmitter systems, including dopamine, norepinephrine, acetylcholine, glutamate, vasopressin, serotonin, γ-aminobutyric acid, and β-endorphins (167, 168). Several animal species, including humans, will self-administer intravenous nicotine in a variety of experimental paradigms, including forced-choice experiments in which they choose nicotine over food (169–177). Nicotine relieves nicotine withdrawal symptoms in abstaining smokers, improves cognitive function in nonsmoking adults (178), and appears to have therapeutic effects in neurodegenerative diseases (179, 180), attention disorders (181), and inflammatory bowel disease (182, 183).

When a person stops smoking abruptly (i.e., "cold turkey"), $\alpha_4\beta_2$-receptor desensitization results in nicotine withdrawal symptoms that are proportional to antecedent objective

measures of dependence severity (184). Nicotine withdrawal can be reliably produced in a number of animal models (185, 186). In humans, symptoms may include anxiety, impaired cognition, difficulty concentrating, irritability, restlessness, depression, or cigarette craving (156, 185, 187–189).

The withdrawal syndrome may directly cause relapse, even after many years of being tobacco free (190–194). In the absence of pharmacotherapy, relapse is often precipitous. More than half of all relapse occurs within 14 days of tobacco use discontinuation, 76% within 30 days, and 96 to 97% within a year (70, 195–197). Approximately 75% of individuals seeking assistance from a physician can be characterized as highly nicotine dependent, up from about 50% in 1990 (198). Consequently, these "hardened" patients are likely to require more intensive treatment, including higher-dose pharmacotherapy, combination pharmacotherapy, more frequent office visits, and longer follow up to control the compulsion to smoke (199). Tobacco dependence can be effectively addressed within the clinic (128, 156, 200–202). The essential clinical paradox is that, although all FDA-approved tobacco-dependence medications are effective in producing abstinence in a dose-dependent fashion (203, 204), practical effectiveness appears to have recently declined because of issues such as underdosing, poor product use technique, and lack of physician guidance (205–207). Attention to proper dosing, treatment duration, and individualized combination pharmacotherapy strategies, coupled with advice to assuage patient concerns regarding side effects (208), can boost abstinence rates from 3 to 6% for unsupported cold-turkey attempts (70, 195, 197) to nearly 60% with full multimodal assistance (209–213).

Novel approaches to treatment and assistance. Multiple venues for potential smoking cessation activities have emerged on social media, particularly Twitter and Facebook. Very little information exists on their relative effectiveness, especially regarding the impact on specific demographic groups like young smokers. Hundreds of cessation apps with content consistent with U.S. Public Health Service Guidelines are available for the two major smartphone platforms (214). No systematic review of the required characteristics or effectiveness of smartphone apps is available. However, early data suggest that mobile devices are feasible for delivering cessation support but appear to move smokers toward quitting less quickly than simple text messaging (215).

The e-cigarette is an emerging phenomenon that is becoming increasingly popular worldwide. This family of devices can generally be described as battery-powered electronic nicotine delivery systems that are made to look very similar to conventional cigarettes, so that users can emulate the smoking behavior (216). Because the e-cigarette does not require "traditional" combustion, it has been frequently postulated that smokers who decide to switch to e-cigarettes instead of continuing to smoke would achieve large health gains (217). Although the device is not overtly marketed as a cessation aid, the majority of e-cigarette use is in an effort to quit or replace cigarettes (218). One-third of respondents explicitly believed them to be safer than conventional cigarettes, and more than 40% indirectly rated them as an acceptable alternative to cigarettes (219–221). The number of U.S. users reached an estimated 2.5 million in 2012, doubling the 2010 estimate (222).

Even if the e-cigarette has the ability to successfully reduce the risk of harm from smoking for individuals within the population, it may still cause harm when viewed from a broader, population perspective. Perhaps most troubling in this regard is the observation that e-cigarette use among U.S. middle and high school students has steadily risen, causing concerns that the device may function as a "gateway" to adolescent nicotine addiction (55, 223). The widespread availability of the device, and its ability to recreate salient cues to smoke, may also trigger smokers trying to quit to continue behaviors that reduce their likelihood of abstinence or trigger former smokers back to behaviors that increase the risk of relapse. For example, in a cross-sectional survey of current or recently former smokers across the United States, no association could be detected between ever use of e-cigarettes and "successful quitter" status, whereas a significant association was identified with "unsuccessful quitter" status (224). Among callers to U.S. quitlines, postintervention follow-up data suggests that e-cigarette use, even for less than 1 month, was significantly associated with a lower likelihood of abstinence 7 months after conventional treatment (218).

Although the overall population impact of e-cigarettes remains uncertain, the potential for alternative nicotine delivery devices to improve the public health is being actively explored (225). Traditional smokeless tobacco has been advocated for harm reduction because it can deliver as much nicotine as cigarettes. However, the products contain significant amounts of carcinogenic nitrosamines and have not yet been proven to promote cessation from cigarettes, raising concern that dual use of smokeless tobacco and cigarettes may inhibit or delay efforts to stop smoking. Newer oral dissolvable tobacco products contain lower levels of toxicants than other smokeless tobacco but deliver much less nicotine and have not been popular with consumers. Norwegian men who used moist snuff (snus) at 16 years of age had an increased risk of smoking 3 years later (226). Dual use of snus and cigarettes was significantly more likely than snus alone, suggesting that snus use in adolescence increases the risk of later smoking. Similar observations regarding alternative tobacco products have been reported from Sweden and the United States (227, 228).

Mindfulness training, based on Buddhist meditative practices of attentiveness, nonjudgmental awareness, and self-acceptance, is effective as a stress-reducing method that tempers psychological stress and improves the sense of well-being (229, 230). This practice may also help people interrupt the harmful automatic behaviors that underlie addiction (231). A preliminary trial of mindfulness training versus standard behavior modification counseling suggested improved abstinence at Week 17 of follow-up (232).

What We Need to Know

Barriers to engagement limit the healthcare system's ability to fundamentally affect tobacco use prevalence and augment the gains achieved in public health over the past 50 years. Some of these obstacles are practical, likely to be solved with due attention to system organization. Interest in systems innovation and dissemination

of new standards is high and is likely to yield further insights into the practical impediments to care. Future work should attempt to understand how complex systems such as healthcare are likely to experience interactions between multiple external drivers. Are they additive? Are some policy combinations infeasible, or counterproductive to broader goals? In addition, attention should be paid to understanding the factors that lead to "satisficed," or bare minimum, responses to system requirements. From the perspective of ongoing health system administration, is any system change always better than no system change?

More subtle and intangible obstacles to engagement also exist. Foremost, dependence is after all the problem at hand and is defined by the irrational compulsion to smoke and the reluctance to stop. What are the subtle ways in which our assumptions about cognition, volition, and readiness influence our approach to care and undermine our effectiveness? Future attention should be paid to the social science insights that might be derived from studying tobacco users as a distinct cultural group. Particular attention should be paid to the unintended consequences of stigma and denormalization of behavior. How do we capitalize on the positive population-wide impact of motivational campaigns, such as graphic warnings and point-of-sale contacts, without amplifying the isolation, shame, and self-loathing that undermines an individual patient's trust in the therapeutic relationship?

Updating professional school curricula to include education about tobacco use and dependence, motivational interviewing, and the chronic illness model of tobacco-dependence treatment will increase the familiarity and confidence of clinicians and is likely to have a lasting influence on their willingness to deliver care for this population. Identifying the appropriate positioning of training within the system of graduated responsibility will help match educational requirements with clinical skill levels. Encouraging health plans and governmental agencies to simplify reimbursement mechanisms, coupled with research into the net effect of these incentive approaches, will be critical to efforts to increase engagement while constraining costs.

Studies of heavy smokers, highly nicotine-dependent patients, or individuals with high baseline serum cotinine levels suggest that such patients are at higher risk of relapse within 30 days of stopping tobacco-dependence medication than their less-dependent counterparts (184, 233, 234). This makes intuitive sense; however, it remains difficult to determine *a priori* who among our patients will benefit from which treatment and for how long. An evolving understanding of the variable nature of nicotine dependence is likely to improve our ability to individualize care, based perhaps on novel biomarkers or other phenotypic characterizations (235, 236).

Although the future of tobacco treatment may belong to the social scientists or the geneticists, there are a number of avenues of inquiry that would be of immediate usefulness to clinicians. For instance, strategies for optimizing the dose, duration, and combination of existing FDA-approved dependence medications could have a transformative effect in the clinic (156, 204). High-throughput models for studying existing medications, approved for other indications but with theoretical application to tobacco dependence, could accelerate our understanding of nicotine addiction treatment and have practical implications on our treatment paradigms. In fact, some of our most glaring knowledge gaps stem from early conceptualization of outcome measures that relate to "cessation" rather than to "control" as with most other chronic illnesses. Development of nonlinear, stochastic models of disease states, reflecting our observations that patterns of tobacco use and control of dependence are not uniform, will help us understand the true impact of adaptive treatment intervention within a population and may more accurately reflect the dynamic, lifelong nature of the illness.

A significant portion of the adolescent population currently uses tobacco, and efforts at both primary prevention and cessation remain of particular public health relevance. Bupropion and nicotine replacement therapies—including nicotine patches, gum, and nasal spray—have been studied to a limited extent in the adolescent population. Although trials suggest long-term quitting is difficult to achieve in adolescent smokers, significant reductions in tobacco consumption have been observed in response to pharmacotherapy (237, 238). In addition to counseling and behavioral interventions, pharmacotherapy should be considered for adolescent patients, individualized to account for smoking patterns and preferences.

It is clear that nicotine withdrawal symptoms cause relapse. Although tobacco-dependence medications are used to minimize the impulsivity of withdrawal, we lack compelling evidence for behavioral interventions' role in reducing the emotional consequences of the compulsion to smoke. Mindfulness meditation may represent one mechanism by which behavioral-modification techniques might be used not only to change responses to compulsion but perhaps also to minimize the psychic drive to smoke. Methods for measuring degree of compulsion and the net effect on treatment outcomes have not yet been identified and will likely require refinement of adaptive intervention modeling in clinical trial design.

The field of tobacco dependence lacks a valid method for differentiating nicotine withdrawal symptoms from treatment side effects. Work to determine the clinically relevant genotypes that affect treatment outcomes and the risk of adverse effects would be beneficial. Standardized methods for estimating the impact of alternative tobacco products such as snus and e-cigarettes on the compulsion to smoke, their intrinsic abuse potential (particularly in recruiting new users), the likelihood of continued smoking, and the probability of side effects or adverse events are warranted.

Future research priorities should seek to clarify the complex relationships between biological and social/environmental determinants of cessation outcomes. For example, strategies aimed at maximizing the nascent impact of social media in altering smoking decision making would be of global value. Real-time ecologic analysis of user interactions, coupled with sophisticated content analysis, may provide a "big data" approach to describing the requirements for effective social media site and smartphone application design. Novel funding mechanisms to stimulate public–private partnerships may help test the promise of emerging technologies within small communities or municipalities.

Discussion

Since the publication of the 1996 ATS statement on tobacco, the world has experienced a period of remarkable growth in insight regarding the nature of the global tobacco epidemic. Although much has been accomplished, significant gaps in understanding remain, and implementation often lags well behind our insights. This report identifies a number of investigative opportunities for significantly reducing the toll of tobacco use. In the coming era of tobacco research, scientists from multiple disciplines will pool their talents and apply increasingly creative analytical methods to further illuminate the complex social, environmental, and biological codeterminants of tobacco use. Curbing the epidemic will require investigating methods that maximize the impact of existing, proven tools as well as identifying novel methods for interrupting the spread of illness.

A number of public and private granting mechanisms have created significant opportunity for scientific exploration. However, both the complexity and the enormity of the tobacco epidemic risk straining existing funding mechanisms unless accommodations are made to encourage innovative, nontraditional solutions to the problem. Government agencies should consider novel ways of leveraging their funds by partnering with similar agencies of other countries in pursuit of global solutions. Both public healthcare financing and private insurance agencies should consider pooling resources to establish funds from which competitive grants might encourage healthcare organizations to assume responsibility for controlling the epidemic within their communities. Public–private partnerships are an appealing way to stimulate innovation and entrepreneurship, and models that make organized efforts to reduce the prevalence of tobacco use financially attractive warrant further exploration. However, given the tobacco industry's historical manipulation of academic research relationships to further its commercial interests (239), research relationships with the tobacco industry should continue to be strongly discouraged by the ATS and other professional societies (240).

Patient Perspective

From the patient's perspective, tobacco use is a frightening proposition. What we do not know about smoking is still more frightening. It was difficult to reconcile being diagnosed with lung cancer more than a decade after quitting. My struggle to quit lasted more than 20 years, and it was always difficult to understand why. Pregnancy should have been a good time to quit, but despite tremendous effort, the best I could do was cut back. My family has experienced a number of difficulties because of smoking, and yet my son grew into adulthood to become a tobacco user himself, engaged in his own fight to quit. To the patient, tobacco use represents a number of unresolved questions. Why is it so hard to quit? How does smoking relieve life's stressors? Have I passed my problem along to my child? Where do I go for help? What should that help look like? This ATS statement serves a critical need in this regard, describing the state of our understanding about these, and many other, important questions. In one document, the report offers readers an essential insight into many parts of the problem, from disciplines as varied as genetics to communication science, important to both researchers and patients alike.

The United States has seen remarkable declines in tobacco use since the landmark 1964 Surgeon General's Report. Yet, each day, more than 3,000 children smoke their first cigarette, and more than half of adult cigarette smokers want to quit but can't. From any perspective, this is an untenable situation. This ATS Research Statement takes an important step forward by compiling data from multiple sources and identifying opportunities for scientists and clinicians to improve the ways they help tobacco-dependent individuals. In particular, the report's emphasis on the disparate impact of tobacco on various at-risk communities, and the discussion of specific barriers to cessation faced by many, represent an important contribution to efforts aimed at reducing inequalities in care. ■

This Research Statement was prepared by the American Thoracic Society Tobacco Action Committee.

Members of the writing committee:

Frank T. Leone, M.D., M.S. (*Chair*)
Kai-Hakon Carlsen, M.D., Ph.D.
Patricia Folan, R.N., D.N.P.
Karen Latzka
Alfred Munzer, M.D.
Enid Neptune, M.D.
Smita Pakhale, M.D., M.Sc.
David P. L. Sachs, M.D.
Jonathan Samet, M.D., M.S.
Dona Upson, M.D.
Alexander White, M.D.

Author Disclosures: K.-H.C. reported serving on an advisory committee for Meda and as a speaker for Boehringer Ingelheim and Takeda Nycomed. F.T.L., P.F., K.L., A.M., E.N., S.P., D.P.L.S., J.S., D.U., and A.W. reported no relevant commercial interests related to the subject matter.

Acknowledgment: The authors thank Mr. Courtney White and Dr. Kevin Wilson for their contributions to this project. Without their implementation assistance and methodological guidance, this group effort would have been impossible.

References

1. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. The health consequences of smoking—50 years of progress: a report of the Surgeon General. Atlanta: Centers for Disease Control and Prevention (US). 2014 [accessed 2014 Apr 13]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK179276/
2. Agaku IT, King BA, Dube SR; Centers for Disease Control and Prevention (CDC). Current cigarette smoking among adults: United States, 2005-2012. *MMWR Morb Mortal Wkly Rep* 2014;63: 29–34.
3. Centers for Disease Control and Prevention (CDC). State-specific prevalence of cigarette smoking and smokeless tobacco use among adults: United States, 2009. *MMWR Morb Mortal Wkly Rep* 2010;59: 1400–1406.
4. World Health Organization. Tobacco fact sheet No. 339. 2013 Jun [updated 2015 May; accessed 2014 Apr 13]. Available from: http://www.who.int/mediacentre/factsheets/fs339/en/

5. World Health Organization. WHO Framework Convention on Tobacco Control. [accessed 2015 Jul 16]. Available from: http://www.who.int/fctc/en/
6. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. Preventing tobacco use among youth and young adults: a report of the Surgeon General. Atlanta: Centers for Disease Control and Prevention (US). 2012 [accessed 2014 Apr 13]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK99237/
7. National Cancer Institute. The role of the media in promoting and reducing tobacco use. Tobacco Control Monograph No. 19. Bethesda, MD: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2008.
8. Mayer KH, Bradford JB, Makadon HJ, Stall R, Goldhammer H, Landers S. Sexual and gender minority health: what we know and what needs to be done. *Am J Public Health* 2008;98:989–995.
9. Lee JGL, Griffin GK, Melvin CL. Tobacco use among sexual minorities in the USA, 1987 to May 2007: a systematic review. *Tob Control* 2009;18:275–282.
10. Kann L, Olsen EO, McManus T, Kinchen S, Chyen D, Harris WA, Wechsler H. Sexual identity, sex of sexual contacts, and health-risk behaviors among students in grades 9–12–youth risk behavior surveillance, selected sites, United States, 2001–2009. *MMWR Surveill Summ* 2011;60:1–133.
11. Matthews AK, Li C–C, Kuhns LM, Tasker TB, Cesario JA. Results from a community-based smoking cessation treatment program for LGBT smokers. *J Environ Public Health* 2013;2013:984508.
12. Reeves WC, Strine TW, Pratt LA, Thompson W, Ahluwalia I, Dhingra SS, McKnight-Eily LR, Harrison L, D'Angelo DV, Williams L, *et al*. Mental illness surveillance among adults in the United States. *MMWR Surveill Summ* 2011;60:1–29.
13. Centers for Disease Control and Prevention (CDC). Vital signs: current cigarette smoking among adults aged ⩾18 years with mental illness - United States, 2009-2011. *MMWR Morb Mortal Wkly Rep* 2013;62:81–87.
14. Banham L, Gilbody S. Smoking cessation in severe mental illness: what works? *Addiction* 2010;105:1176–1189.
15. Williams JM, Foulds J. Successful tobacco dependence treatment in schizophrenia. *Am J Psychiatry* 2007;164:222–227, quiz 373.
16. Tsoi DT, Porwal M, Webster AC. Interventions for smoking cessation and reduction in individuals with schizophrenia. *Cochrane Database Syst Rev* 2013;2:CD007253.
17. Williams JM, Anthenelli RM, Morris CD, Treadow J, Thompson JR, Yunis C, George TP. A randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of varenicline for smoking cessation in patients with schizophrenia or schizoaffective disorder. *J Clin Psychiatry* 2012;73:654–660.
18. Cavazos-Rehg PA, Breslau N, Hatsukami D, Krauss MJ, Spitznagel EL, Grucza RA, Salyer P, Hartz SM, Bierut LJ. Smoking cessation is associated with lower rates of mood/anxiety and alcohol use disorders. *Psychol Med* 2014;44:2523–2535.
19. Bolam B, West R, Gunnell D. Does smoking cessation cause depression and anxiety? Findings from the ATTEMPT cohort. *Nicotine Tob Res* 2011;13:209–214.
20. Glaze L. Correctional populations in the United States, 2010. 2011 Dec [accessed 2014 Apr 13]. Available from: www.bjs.gov/content/pub/pdf/cpus10.pdf
21. Cropsey KL, Jones-Whaley S, Jackson DO, Hale GJ. Smoking characteristics of community corrections clients. *Nicotine Tob Res* 2010;12:53–58.
22. Cropsey K, Eldridge G, Weaver M, Villalobos G, Stitzer M, Best A. Smoking cessation intervention for female prisoners: addressing an urgent public health need. *Am J Public Health* 2008;98:1894–1901.
23. US Census Bureau. Income, poverty and health insurance coverage in the United States: 2012. Income & wealth - newsroom [accessed 2015 Jul 16]. Available from: http://www.census.gov/newsroom/releases/archives/income_wealth/cb13-165.html
24. Centers for Disease Control and Prevention (CDC). Current cigarette smoking among adults: United States, 2011. *MMWR Morb Mortal Wkly Rep* 2012;61:889–894.
25. Baggett TP, Tobey ML, Rigotti NA. Tobacco use among homeless people: addressing the neglected addiction. *N Engl J Med* 2013; 369:201–204.
26. Brown DW. Smoking prevalence among US veterans. *J Gen Intern Med* 2010;25:147–149.
27. The Office of Adolescent Health. US Department of Health and Human Services. Office of Adolescent Health [accessed 2015 Jul 16]. Available from: http://www.hhs.gov/ash/oah/
28. Hale D, Viner R. Trends in the prevalence of multiple substance use in adolescents in England, 1998-2009. *J Public Health (Oxf)* 2013;35: 367–374.
29. Konfino J, Ferrante D, Goldberg L, Caixeta R, Palipudi KM; Centers for Disease Control and Prevention. Tobacco use among youths: Argentina, 2007 and 2012. *MMWR Morb Mortal Wkly Rep* 2014;63: 588–590.
30. Centers for Disease Control and Prevention (CDC). Current tobacco use among middle and high school students: United States, 2011. *MMWR Morb Mortal Wkly Rep* 2012;61:581–585.
31. Centers for Disease Control and Prevention (CDC). High school students who tried to quit smoking cigarettes: United States, 2007. *MMWR Morb Mortal Wkly Rep* 2009;58:428–431.
32. Stanton A, Grimshaw G. Tobacco cessation interventions for young people. *Cochrane Database Syst Rev* 2013;8:CD003289.
33. Lovato C, Watts A, Stead LF. Impact of tobacco advertising and promotion on increasing adolescent smoking behaviours. *Cochrane Database Syst Rev* 2011;10:CD003439.
34. Morgenstern M, Sargent JD, Isensee B, Hanewinkel R. From never to daily smoking in 30 months: the predictive value of tobacco and non-tobacco advertising exposure. *BMJ Open* 2013;3.
35. Paynter J, Edwards R. The impact of tobacco promotion at the point of sale: a systematic review. *Nicotine Tob Res* 2009;11:25–35.
36. Henriksen L. Comprehensive tobacco marketing restrictions: promotion, packaging, price and place. *Tob Control* 2012;21: 147–153.
37. Clattenburg EJ, Elf JL, Apelberg BJ. Unplanned cigarette purchases and tobacco point of sale advertising: a potential barrier to smoking cessation. *Tob Control* 2013;22:376–381.
38. Henriksen L, Feighery EC, Schleicher NC, Haladjian HH, Fortmann SP. Reaching youth at the point of sale: cigarette marketing is more prevalent in stores where adolescents shop frequently. *Tob Control* 2004;13:315–318.
39. Lovato CY, Hsu HCH, Sabiston CM, Hadd V, Nykiforuk CIJ. Tobacco point-of-purchase marketing in school neighbourhoods and school smoking prevalence: a descriptive study. *Can J Public Health* 2007;98:265–270.
40. Dauphinee AL, Doxey JR, Schleicher NC, Fortmann SP, Henriksen L. Racial differences in cigarette brand recognition and impact on youth smoking. *BMC Public Health* 2013;13:170.
41. Duke JC, Allen JA, Pederson LL, Mowery PD, Xiao H, Sargent JD. Reported exposure to pro-tobacco messages in the media: trends among youth in the United States, 2000-2004. *Am J Health Promot* 2009;23:195–202.
42. Jenssen BP, Klein JD, Salazar LF, Daluga NA, DiClemente RJ. Exposure to tobacco on the Internet: content analysis of adolescents' Internet use. *Pediatrics* 2009;124:e180–e186.
43. Forsyth SR, Kennedy C, Malone RE. The effect of the Internet on teen and young adult tobacco use: a literature review. *J Pediatr Health Care* 2013;27:367–376.
44. Proctor R. Golden holocaust: origins of the cigarette catastrophe and the case for abolition. Berkeley, CA: University of California Press; 2012.
45. Sargent JD, Beach ML, Adachi-Mejia AM, Gibson JJ, Titus-Ernstoff LT, Carusi CP, Swain SD, Heatherton TF, Dalton MA. Exposure to movie smoking: its relation to smoking initiation among US adolescents. *Pediatrics* 2005;116:1183–1191.
46. Morgenstern M, Sargent JD, Engels RCME, Scholte RHJ, Florek E, Hunt K, Sweeting H, Mathis F, Faggiano F, Hanewinkel R. Smoking in movies and adolescent smoking initiation: longitudinal study in six European countries. *Am J Prev Med* 2013;44:339–344.
47. Glantz SA, Iaccopucci A, Titus K, Polansky JR. Smoking in top-grossing US movies, 2011. *Prev Chronic Dis* 2012;9:120170.
48. National Association of Attorneys General. Movie studios should stop depicting smoking in youth-rated movies [accessed 2015 Jul 16]. Available from: http://www.naag.org/naag/media/naag-news/movie-studios-should-stop-depicting-smoking-in-youth-rated-movies.php
49. Centers for Disease Control and Prevention. Fact sheet. Smoking in the movies: smoking & tobacco use [accessed 2015 Jul 16].

Available from: http://www.cdc.gov/tobacco/data_statistics/fact_sheets/youth_data/movies/index.htm
50. Lee JGL, Agnew-Brune CB, Clapp JA, Blosnich JR. Out smoking on the big screen: tobacco use in LGBT movies, 2000–2011. *Tob Control* 2014;23:e156–e158.
51. Dal Cin S, Stoolmiller M, Sargent JD. Exposure to smoking in movies and smoking initiation among black youth. *Am J Prev Med* 2013; 44:345–350.
52. Tanski SE, Stoolmiller M, Gerrard M, Sargent JD. Moderation of the association between media exposure and youth smoking onset: race/ethnicity, and parent smoking. *Prev Sci* 2012;13:55–63.
53. Wilkinson AV, Spitz MR, Prokhorov AV, Bondy ML, Shete S, Sargent JD. Exposure to smoking imagery in the movies and experimenting with cigarettes among Mexican heritage youth. *Cancer Epidemiol Biomarkers Prev* 2009;18:3435–3443.
54. DiFranza JR, Savageau JA, Fletcher K, O'Loughlin J, Pbert L, Ockene JK, McNeill AD, Hazelton J, Friedman K, Dussault G, *et al*. Symptoms of tobacco dependence after brief intermittent use: the Development and Assessment of Nicotine Dependence in Youth-2 study. *Arch Pediatr Adolesc Med* 2007;161:704–710.
55. Centers for Disease Control and Prevention (CDC). Tobacco product use among middle and high school students: United States, 2011 and 2012. *MMWR Morb Mortal Wkly Rep* 2013;62:893–897.
56. U.S. Food and Drug Administration. Press announcements: FDA proposes to extend its tobacco authority to additional tobacco products, including e-cigarettes. 2014 Apr 24 [accessed 2014 May 16]. Available from: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm394667.htm
57. Hatzenbuehler ML, Phelan JC, Link BG. Stigma as a fundamental cause of population health inequalities. *Am J Public Health* 2013; 103:813–821.
58. Reducing Tobacco Use. Reducing tobacco use: a report of the Surgeon General. Executive Summary. *MMWR Recomm Rep* 2000;49:1–27.
59. Blosnich JR, Farmer GW, Lee JGL, Silenzio VMB, Bowen DJ. Health inequalities among sexual minority adults: evidence from ten U.S. states, 2010. *Am J Prev Med* 2014;46:337–349.
60. Corliss HL, Wadler BM, Jun H-J, Rosario M, Wypij D, Frazier AL, Austin SB. Sexual-orientation disparities in cigarette smoking in a longitudinal cohort study of adolescents. *Nicotine Tob Res* 2013;15:213–222.
61. Blosnich JR, Horn K. Associations of discrimination and violence with smoking among emerging adults: differences by gender and sexual orientation. *Nicotine Tob Res* 2011;13: 1284–1295.
62. Blosnich J, Lee JGL, Horn K. A systematic review of the aetiology of tobacco disparities for sexual minorities. *Tob Control* 2013;22:66–73.
63. Rosario M, Schrimshaw EW, Hunter J. Disclosure of sexual orientation and subsequent substance use and abuse among lesbian, gay, and bisexual youths: critical role of disclosure reactions. *Psychol Addict Behav* 2009;23:175–184.
64. Moskowitz A, Stein JA, Lightfoot M. The mediating roles of stress and maladaptive behaviors on self-harm and suicide attempts among runaway and homeless youth. *J Youth Adolesc* 2013;42: 1015–1027.
65. Stevens P, Carlson LM, Hinman JM. An analysis of tobacco industry marketing to lesbian, gay, bisexual, and transgender (LGBT) populations: strategies for mainstream tobacco control and prevention. *Health Promot Pract* 2004;5:129S–134S.
66. Smith EA, Thomson K, Offen N, Malone RE. "If you know you exist, it's just marketing poison": meanings of tobacco industry targeting in the lesbian, gay, bisexual, and transgender community. *Am J Public Health* 2008;98:996–1003.
67. Penaloza L. We're here, we're queer, and we're going shopping! A critical perspective on the accommodation of gays and lesbians in the US marketplace. In: Wardlow DL, ed. Gays, lesbians, and consumer behavior: theory, practice and research issues in marketing. New York: Haworth; 1996. pp. 9–41.
68. Institute of Medicine. The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Institute of Medicine [accessed 2015 Jul 16]. Available from: http://www.iom.edu/Reports/2011/The-Health-of-Lesbian-Gay-Bisexual-and-Transgender-People.aspx
69. Centers for Disease Control and Prevention (US), National Center for Chronic Disease Prevention and Health Promotion (US), Office on Smoking and Health (US). How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease: a report of the Surgeon General. Atlanta: Centers for Disease Control and Prevention (US). 2010 [accessed 2014 Apr 14]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK53017/
70. Benowitz NL. Nicotine addiction. *N Engl J Med* 2010;362:2295–2303.
71. Rossing MA. Genetic influences on smoking: candidate genes. *Environ Health Perspect* 1998;106:231–238.
72. Shiffman S. Refining models of dependence: variations across persons and situations. *Br J Addict* 1991;86:611–615.
73. Sargent JD, Hanewinkel R. Comparing the effects of entertainment media and tobacco marketing on youth smoking in Germany. *Addiction* 2009;104:815–823.
74. Sargent JD, Gibson J, Heatherton TF. Comparing the effects of entertainment media and tobacco marketing on youth smoking. *Tob Control* 2009;18:47–53.
75. Titus-Ernstoff L, Dalton MA, Adachi-Mejia AM, Longacre MR, Beach ML. Longitudinal study of viewing smoking in movies and initiation of smoking by children. *Pediatrics* 2008;121:15–21.
76. Coady MH, Chan CA, Auer K, Farley SM, Kilgore EA, Kansagra SM. Awareness and impact of New York City's graphic point-of-sale tobacco health warning signs. *Tob Control* 2013;22:e51–e56.
77. Hammond D, Fong GT, Borland R, Cummings KM, McNeill A, Driezen P. Text and graphic warnings on cigarette packages: findings from the international tobacco control four country study. *Am J Prev Med* 2007;32:202–209.
78. Centers for Disease Control and Prevention (CDC). Cigarette package health warnings and interest in quitting smoking: 14 countries, 2008–2010. *MMWR Morb Mortal Wkly Rep* 2011;60:645–651.
79. Disc. Tobacco City & Lottery, Inc. v. United States. Justia Law [accessed 2015 Jul 16]. Available from: http://law.justia.com/cases/federal/appellate-courts/ca6/10-5235/10-5235-2012-03-19.html
80. Gilpin EA, White MM, Messer K, Pierce JP. Receptivity to tobacco advertising and promotions among young adolescents as a predictor of established smoking in young adulthood. *Am J Public Health* 2007;97:1489–1495.
81. Germain D, Wakefield MA, Durkin SJ. Adolescents' perceptions of cigarette brand image: does plain packaging make a difference? *J Adolesc Health* 2010;46:385–392.
82. Farrelly MC, Nonnemaker J, Davis KC, Hussin A. The Influence of the National Truth Campaign on smoking initiation. *Am J Prev Med* 2009;36:379–384.
83. Gladwell M. The tipping point : how little things can make a big difference, 1st ed. Boston: Little, Brown; 2000.
84. National Cancer Institute. Greater than the sum: systems thinking in tobacco control. Tobacco Control Monograph No. 18. Bethesda, MD: US Department of Health and Human Services, National Institutes of Health, National Cancer Institute; 2007.
85. Surgeon General's Advisory Committee on Smoking and Health. United States Public Health Service, Office of the Surgeon General. Smoking and health. Public Health Service Publication No. 1103. 1964 [accessed 2013 Nov 19]. Available from: http://profiles.nlm.nih.gov/NN/B/B/M/Q/
86. United States Public Health Service, Office on Smoking and Health. United States Public Health Service, Office of the Surgeon General. The health consequences of involuntary smoking: a report of the Surgeon General. Department of Health and Human Services Publication No. (CDC) 87–8398. 1986 [accessed 2014 Apr 14]. Available from: http://profiles.nlm.nih.gov/NN/B/C/P/M/
87. Wang X, Tager IB, Van Vunakis H, Speizer FE, Hanrahan JP. Maternal smoking during pregnancy, urine cotinine concentrations, and birth outcomes. A prospective cohort study. *Int J Epidemiol* 1997; 26:978–988.
88. Bastek JA, Sammel MD, Srinivas SK, McShea MA, Foreman MN, Elovitz MA, Metlay JP. Clinical prediction rules for preterm birth in patients presenting with preterm labor. *Obstet Gynecol* 2012;119: 1119–1128.
89. Martinez FD, Wright AL, Taussig LM; Group Health Medical Associates. The effect of paternal smoking on the birthweight of

newborns whose mothers did not smoke. *Am J Public Health* 1994; 84:1489–1491.
90. Hackshaw A, Rodeck C, Boniface S. Maternal smoking in pregnancy and birth defects: a systematic review based on 173 687 malformed cases and 11.7 million controls. *Hum Reprod Update* 2011;17:589–604.
91. Anderson HR, Cook DG. Passive smoking and sudden infant death syndrome: review of the epidemiological evidence. *Thorax* 1997; 52:1003–1009.
92. Elliot J, Vullermin P, Robinson P. Maternal cigarette smoking is associated with increased inner airway wall thickness in children who die from sudden infant death syndrome. *Am J Respir Crit Care Med* 1998;158:802–806.
93. Tager IB, Ngo L, Hanrahan JP. Maternal smoking during pregnancy. Effects on lung function during the first 18 months of life. *Am J Respir Crit Care Med* 1995;152:977–983.
94. Lødrup Carlsen KC, Jaakkola JJ, Nafstad P, Carlsen KH. In utero exposure to cigarette smoking influences lung function at birth. *Eur Respir J* 1997;10:1774–1779.
95. Hoo AF, Henschen M, Dezateux C, Costeloe K, Stocks J. Respiratory function among preterm infants whose mothers smoked during pregnancy. *Am J Respir Crit Care Med* 1998;158:700–705.
96. Sekhon HS, Keller JA, Benowitz NL, Spindel ER. Prenatal nicotine exposure alters pulmonary function in newborn rhesus monkeys. *Am J Respir Crit Care Med* 2001;164:989–994.
97. Sekhon HS, Keller JA, Proskocil BJ, Martin EL, Spindel ER. Maternal nicotine exposure upregulates collagen gene expression in fetal monkey lung: association with alpha7 nicotinic acetylcholine receptors. *Am J Respir Cell Mol Biol* 2002;26:31–41.
98. Maritz GS, Dennis H. Maternal nicotine exposure during gestation and lactation interferes with alveolar development in the neonatal lung. *Reprod Fertil Dev* 1998;10:255–261.
99. Sekhon HS, Jia Y, Raab R, Kuryatov A, Pankow JF, Whitsett JA, Lindstrom J, Spindel ER. Prenatal nicotine increases pulmonary alpha7 nicotinic receptor expression and alters fetal lung development in monkeys. *J Clin Invest* 1999;103:637–647.
100. Wongtrakool C, Roser-Page S, Rivera HN, Roman J. Nicotine alters lung branching morphogenesis through the α7 nicotinic acetylcholine receptor. *Am J Physiol Lung Cell Mol Physiol* 2007; 293:L611–L618.
101. Gilliland FD, Berhane K, Li Y-F, Rappaport EB, Peters JM. Effects of early onset asthma and in utero exposure to maternal smoking on childhood lung function. *Am J Respir Crit Care Med* 2003;167: 917–924.
102. Wang C, Salam MT, Islam T, Wenten M, Gauderman WJ, Gilliland FD. Effects of in utero and childhood tobacco smoke exposure and beta2-adrenergic receptor genotype on childhood asthma and wheezing. *Pediatrics* 2008;122:e107–e114.
103. Breton CV, Salam MT, Gilliland FD. Heritability and role for the environment in DNA methylation in AXL receptor tyrosine kinase. *Epigenetics* 2011;6:895–898.
104. Terry MB, Ferris JS, Pilsner R, Flom JD, Tehranifar P, Santella RM, Gamble MV, Susser E. Genomic DNA methylation among women in a multiethnic New York City birth cohort. *Cancer Epidemiol Biomarkers Prev* 2008;17:2306–2310.
105. Li Y-F, Langholz B, Salam MT, Gilliland FD. Maternal and grandmaternal smoking patterns are associated with early childhood asthma. *Chest* 2005;127:1232–1241.
106. Baba S, Wikström A-K, Stephansson O, Cnattingius S. Influence of smoking and snuff cessation on risk of preterm birth. *Eur J Epidemiol* 2012;27:297–304.
107. Schneider S, Schütz J. Who smokes during pregnancy? A systematic literature review of population-based surveys conducted in developed countries between 1997 and 2006. *Eur J Contracept Reprod Health Care* 2008;13:138–147.
108. Al-Sahab B, Saqib M, Hauser G, Tamim H. Prevalence of smoking during pregnancy and associated risk factors among Canadian women: a national survey. *BMC Pregnancy Childbirth* 2010; 10:24.
109. Erickson AC, Arbour LT. Heavy smoking during pregnancy as a marker for other risk factors of adverse birth outcomes: a population-based study in British Columbia, Canada. *BMC Public Health* 2012;12:102.
110. Tong VT, Dietz PM, England LJ, Farr SL, Kim SY, D'Angelo D, Bombard JM. Age and racial/ethnic disparities in prepregnancy smoking among women who delivered live births. *Prev Chronic Dis* 2011;8:A121.
111. Centers for Disease Control and Prevention. Tobacco use and pregnancy: reproductive health [accessed 2015 Jul 16]. Available from: http://www.cdc.gov/reproductivehealth/TobaccoUsePregnancy/
112. Cnattingius S. The epidemiology of smoking during pregnancy: smoking prevalence, maternal characteristics, and pregnancy outcomes. *Nicotine Tob Res* 2004;6:S125–S140.
113. Atrash HK, Hughes JM, Hogue CJ. Ectopic pregnancy in the United States, 1970–1983. *MMWR CDC Surveill Summ* 1986;35: 29SS–37SS.
114. Office on Smoking and Health (US). Women and smoking: a report of the Surgeon General. Atlanta: Centers for Disease Control and Prevention (US). 2001 [accessed 2014 May 14]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK44303/
115. Svensson AC, Pawitan Y, Cnattingius S, Reilly M, Lichtenstein P. Familial aggregation of small-for-gestational-age births: the importance of fetal genetic effects. *Am J Obstet Gynecol* 2006; 194:475–479.
116. Ananth CV, Savitz DA, Luther ER. Maternal cigarette smoking as a risk factor for placental abruption, placenta previa, and uterine bleeding in pregnancy. *Am J Epidemiol* 1996;144:881–889.
117. Faruque MO, Khan MR, Rahman MM, Ahmed F. Relationship between smoking and antioxidant nutrient status. *Br J Nutr* 1995; 73:625–632.
118. Centers for Disease Control and Prevention. Patterns of tobacco use among women and girls. Smoking and tobacco use [accessed 2015 Jul 16]. Available from: http://www.cdc.gov/tobacco/data_statistics/sgr/2001/highlights/tobaccouse/
119. Aydogan U, Durmaz E, Ercan CM, Eken A, Ulutas OK, Kavuk S, Gursel O, Alanbay I, Akay C, Kurekci AE, *et al*. Effects of smoking during pregnancy on DNA damage and ROS level consequences in maternal and newborns' blood. *Arh Hig Rada Toksikol* 2013;64: 35–46.
120. Chelchowska M, Ambroszkiewicz J, Gajewska J, Laskowska-Klita T, Leibschang J. The effect of tobacco smoking during pregnancy on plasma oxidant and antioxidant status in mother and newborn. *Eur J Obstet Gynecol Reprod Biol* 2011;155:132–136.
121. Chełchowska M, Jabłonka-Salach K, Ambroszkiewicz J, Maciejewski T, Gajewska J, Bulska E, Laskowska-Klita T, Leibschang J, Barciszewski J. Effect of cigarette smoking on blood lead levels in pregnant women [in Polish]. *Med Wieku Rozwoj* 2012;16:196–204.
122. Banihosseini SZ, Baheiraei A, Shirzad N, Heshmat R, Mohsenifar A. The effect of cigarette smoke exposure on vitamin D level and biochemical parameters of mothers and neonates. *J Diabetes Metab Disord* 2013;12:19.
123. Vio F, Salazar G, Infante C. Smoking during pregnancy and lactation and its effects on breast-milk volume. *Am J Clin Nutr* 1991;54: 1011–1016.
124. Etem Pişkin İ, Nur Karavar H, Araslı M, Ermiş B. Effect of maternal smoking on colostrum and breast milk cytokines. *Eur Cytokine Netw* 2012;23:187–190.
125. Schneider S, Huy C, Schütz J, Diehl K. Smoking cessation during pregnancy: a systematic literature review. *Drug Alcohol Rev* 2010; 29:81–90.
126. Lumley J, Chamberlain C, Dowswell T, Oliver S, Oakley L, Watson L. Interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev* 2009;3:CD001055.
127. Coleman T, Chamberlain C, Davey M-A, Cooper SE, Leonardi-Bee J. Pharmacological interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev* 2012; 9:CD010078.
128. Fiore M, Jaén C, Baker T, *et al*. Treating tobacco use and dependence: 2008 update. Clinical Practice Guideline. Rockville, MD: US Department of Health and Human Services. Public Health Service; 2008.

129. Kruger J, Shaw L, Kahende J, Frank E. Health care providers' advice to quit smoking, National Health Interview Survey, 2000, 2005, and 2010. *Prev Chronic Dis* 2012;9:E130.
130. Bernstein SL, Yu S, Post LA, Dziura J, Rigotti NA. Undertreatment of tobacco use relative to other chronic conditions. *Am J Public Health* 2013;103:e59–e65.
131. Conroy MB, Majchrzak NE, Regan S, Silverman CB, Schneider LI, Rigotti NA. The association between patient-reported receipt of tobacco intervention at a primary care visit and smokers' satisfaction with their health care. *Nicotine Tob Res* 2005;7: S29–S34.
132. Stead LF, Bergson G, Lancaster T. Physician advice for smoking cessation. *Cochrane Database Syst Rev* 2008;2:CD000165.
133. Woods SS, Jaén CR. Increasing consumer demand for tobacco treatments: ten design recommendations for clinicians and healthcare systems. *Am J Prev Med* 2010;38:S385–S392.
134. Bryant J, Bonevski B, Paul C, O'Brien J, Oakes W. Developing cessation interventions for the social and community service setting: a qualitative study of barriers to quitting among disadvantaged Australian smokers. *BMC Public Health* 2011;11:493.
135. Mann-Wrobel MC, Bennett ME, Weiner EE, Buchanan RW, Ball MP. Smoking history and motivation to quit in smokers with schizophrenia in a smoking cessation program. *Schizophr Res* 2011;126:277–283.
136. Roddy E, Antoniak M, Britton J, Molyneux A, Lewis S. Barriers and motivators to gaining access to smoking cessation services amongst deprived smokers—a qualitative study. *BMC Health Serv Res* 2006;6:147.
137. Ferguson SG, Gitchell JG, Shiffman S, Sembower MA, Rohay JM, Allen J. Providing accurate safety information may increase a smoker's willingness to use nicotine replacement therapy as part of a quit attempt. *Addict Behav* 2011;36:713–716.
138. Secondhand smoke: awareness, attitudes and exposure among Wisconsin residents [accessed 2015 Jul 16]. Available from: http://www.ctri.wisc.edu/Publications/publications/Secondhandsmoke.pdf
139. Czarnecki KD, Vichinsky LE, Ellis JA, Perl SB. Media campaign effectiveness in promoting a smoking-cessation program. *Am J Prev Med* 2010;38:S333–S342.
140. Pipe A, Sorensen M, Reid R. Physician smoking status, attitudes toward smoking, and cessation advice to patients: an international survey. *Patient Educ Couns* 2009;74:118–123.
141. Ceraso M, McElroy JA, Kuang X, Vila PM, Du X, Lu L, Ren H, Qian N, Jorenby DE, Fiore MC. Smoking, barriers to quitting, and smoking-related knowledge, attitudes, and patient practices among male physicians in China. *Prev Chronic Dis* 2009;6:A06.
142. Tong EK, Strouse R, Hall J, Kovac M, Schroeder SA. National survey of U.S. health professionals' smoking prevalence, cessation practices, and beliefs. *Nicotine Tob Res* 2010;12:724–733.
143. Stead M, Angus K, Holme I, Cohen D, Tait G; PESCE European Research Team. Factors influencing European GPs' engagement in smoking cessation: a multi-country literature review. *Br J Gen Pract* 2009;59:682–690.
144. Weiner B. On sin versus sickness: a theory of perceived responsibility and social motivation. *Am Psychol* 1993;48: 957–965.
145. Brewin CR. Perceived controllability of life-events and willingness to prescribe psychotropic drugs. *Br J Soc Psychol* 1984;23: 285–287.
146. Weiner B. An attributional theory of achievement motivation and emotion. *Psychol Rev* 1985;92:548–573.
147. Weiner B, Perry RP, Magnusson J. An attributional analysis of reactions to stigmas. *J Pers Soc Psychol* 1988;55:738–748.
148. Legacy Tobacco Documents Library. Ammonia [accessed 2015 Jul 16]. Available from: http://legacy.library.ucsf.edu/tid/gfx65d00
149. Legacy Tobacco Documents Library. Root technology: a handbook for leaf binders [accessed 2015 Jul 16]. Available from: http://legacy.library.ucsf.edu/tid/dlh01c00
150. Ferris Wayne G, Connolly GN, Henningfield JE. Brand differences of free-base nicotine delivery in cigarette smoke: the view of the tobacco industry documents. *Tob Control* 2006;15:189–198.
151. Pankow JF, Tavakoli AD, Luo W, Isabelle LM. Percent free base nicotine in the tobacco smoke particulate matter of selected commercial and reference cigarettes. *Chem Res Toxicol* 2003;16: 1014–1018.
152. Lunell E, Molander L, Ekberg K, Wahren J. Site of nicotine absorption from a vapour inhaler: comparison with cigarette smoking. *Eur J Clin Pharmacol* 2000;55:737–741.
153. Leone FT, Evers-Casey S. Developing a rational approach to tobacco use treatment in pulmonary practice: a review of the biological basis of nicotine addiction. *Clin Pulm Med* 2012;19:53–61.
154. Alcaro A, Huber R, Panksepp J. Behavioral functions of the mesolimbic dopaminergic system: an affective neuroethological perspective. *Brain Res Brain Res Rev* 2007;56:283–321.
155. Henningfield JE. Behavioral pharmacology of cigarette smoking. In: Thompson T, Dews PB, Barrett JE, editors. Advances in behavioral pharmacology. Orlando, FL: Academic Press; 1984. pp. 131–210.
156. Sachs D, Leone F, Farber H, Bars M, Prezant D, Schane R, Graham L, Zelman-Lewis S. ACCP tobacco dependence treatment toolkit. American College of Chest Physicians tobacco-dependence treatment tool kit, 3rd ed. [accessed 2015 Jul 16]. Available from: http://tobaccodependence.chestnet.org
157. Menossi HS, Goudriaan AE, de Azevedo-Marques Périco C, Nicastri S, de Andrade AG, D'Elia G, Li CS, Castaldelli-Maia JM. Neural bases of pharmacological treatment of nicotine dependence - insights from functional brain imaging: a systematic review. *CNS Drugs* 2013;27:921–941.
158. Lerman C, Berrettini W. Elucidating the role of genetic factors in smoking behavior and nicotine dependence. *Am J Med Genet B Neuropsychiatr Genet* 2003;118B:48–54.
159. Picciotto MR, Addy NA, Mineur YS, Brunzell DH. It is not "either/or": activation and desensitization of nicotinic acetylcholine receptors both contribute to behaviors related to nicotine addiction and mood. *Prog Neurobiol* 2008;84:329–342.
160. Marks MJ, Burch JB, Collins AC. Effects of chronic nicotine infusion on tolerance development and nicotinic receptors. *J Pharmacol Exp Ther* 1983;226:817–825.
161. Marks MJ, Stitzel JA, Collins AC. Time course study of the effects of chronic nicotine infusion on drug response and brain receptors. *J Pharmacol Exp Ther* 1985;235:619–628.
162. Schwartz RD, Kellar KJ. Nicotinic cholinergic receptor binding sites in the brain: regulation in vivo. *Science* 1983;220:214–216.
163. Schwartz RD, Kellar KJ. In vivo regulation of [3H]acetylcholine recognition sites in brain by nicotinic cholinergic drugs. *J Neurochem* 1985;45:427–433.
164. Benwell ME, Balfour DJ, Anderson JM. Evidence that tobacco smoking increases the density of (-)-[3H]nicotine binding sites in human brain. *J Neurochem* 1988;50:1243–1247.
165. Perry DC, Dávila-García MI, Stockmeier CA, Kellar KJ. Increased nicotinic receptors in brains from smokers: membrane binding and autoradiography studies. *J Pharmacol Exp Ther* 1999;289: 1545–1552.
166. Breese CR, Marks MJ, Logel J, Adams CE, Sullivan B, Collins AC, Leonard S. Effect of smoking history on [3H]nicotine binding in human postmortem brain. *J Pharmacol Exp Ther* 1997;282:7–13.
167. Nisell M, Nomikos GG, Svensson TH. Infusion of nicotine in the ventral tegmental area or the nucleus accumbens of the rat differentially affects accumbal dopamine release. *Pharmacol Toxicol* 1994;75:348–352.
168. Kellar KJ, Dávila-García MI, Xiao Y. Pharmacology of neuronal nicotinic acetylcholine receptors: effects of acute and chronic nicotine. *Nicotine Tob Res* 1999;1:S117–120. [Discussion pp. S139–140.]
169. Henningfield JE. Measurement issues in cigarette smoking research: basic behavioral and physiological effects and patterns of nicotine self-administration. *NIDA Res Monogr* 1983;48:27–38.
170. Goldberg SR, Henningfield JE. Reinforcing effects of nicotine in humans and experimental animals responding under intermittent schedules of i.v. drug injection. *Pharmacol Biochem Behav* 1988; 30:227–234.
171. Rose JE, Sampson A, Levin ED, Henningfield JE. Mecamylamine increases nicotine preference and attenuates nicotine discrimination. *Pharmacol Biochem Behav* 1989;32:933–938.

172. Henningfield JE, Miyasato K, Jasinski DR. Cigarette smokers self-administer intravenous nicotine. *Pharmacol Biochem Behav* 1983;19:887–890.
173. Ator NA, Griffiths RR. Nicotine self-administration in baboons. *Pharmacol Biochem Behav* 1983;19:993–1003.
174. Goldberg SR, Spealman RD, Risner ME, Henningfield JE. Control of behavior by intravenous nicotine injections in laboratory animals. *Pharmacol Biochem Behav* 1983;19:1011–1020.
175. Henningfield JE, Goldberg SR. Control of behavior by intravenous nicotine injections in human subjects. *Pharmacol Biochem Behav* 1983;19:1021–1026.
176. Henningfield JE, Goldberg SR. Nicotine as a reinforcer in human subjects and laboratory animals. *Pharmacol Biochem Behav* 1983;19:989–992.
177. Hall BJ, Pearson LS, Buccafusco JJ. Effect of administration of the nicotinic acetylcholine receptor antagonist BTMPS, during nicotine self-administration, on lever responding induced by context long after withdrawal. *Neuropharmacology* 2010;58: 429–435.
178. Wignall ND, de Wit H. Effects of nicotine on attention and inhibitory control in healthy nonsmokers. *Exp Clin Psychopharmacol* 2011; 19:183–191.
179. Fagerström KO, Pomerleau O, Giordani B, Stelson F. Nicotine may relieve symptoms of Parkinson's disease. *Psychopharmacology (Berl)* 1994;116:117–119.
180. Newhouse P, Kellar K, Aisen P, White H, Wesnes K, Coderre E, Pfaff A, Wilkins H, Howard D, Levin ED. Nicotine treatment of mild cognitive impairment: a 6-month double-blind pilot clinical trial. *Neurology* 2012;78:91–101.
181. Potter AS, Newhouse PA. Acute nicotine improves cognitive deficits in young adults with attention-deficit/hyperactivity disorder. *Pharmacol Biochem Behav* 2008;88:407–417.
182. Pullan RD, Rhodes J, Ganesh S, Mani V, Morris JS, Williams GT, Newcombe RG, Russell MA, Feyerabend C, Thomas GA, *et al*. Transdermal nicotine for active ulcerative colitis. *N Engl J Med* 1994;330:811–815.
183. Pullan RD. Colonic mucus, smoking and ulcerative colitis. *Ann R Coll Surg Engl* 1996;78:85–91.
184. Killen JD, Fortmann SP, Telch MJ, Newman B. Are heavy smokers different from light smokers? A comparison after 48 hours without cigarettes. *JAMA* 1988;260:1581–1585.
185. Hildebrand BE, Nomikos GG, Bondjers C, Nisell M, Svensson TH. Behavioral manifestations of the nicotine abstinence syndrome in the rat: peripheral versus central mechanisms. *Psychopharmacology (Berl)* 1997;129:348–356.
186. Hildebrand BE, Panagis G, Svensson TH, Nomikos GG. Behavioral and biochemical manifestations of mecamylamine-precipitated nicotine withdrawal in the rat: role of nicotinic receptors in the ventral tegmental area. *Neuropsychopharmacology* 1999;21: 560–574.
187. Herning RI, Jones RT, Bachman J. EEG changes during tobacco withdrawal. *Psychophysiology* 1983;20:507–512.
188. Henningfield J, Keenan R, Clarke P. Nicotine. In: Schuster CR, Kuhar MJ, editors. Pharmacological aspects of drug dependence: toward an integrated neurobehavioral approach. Berlin: Springer-Verlag; 1996. pp. 271–314.
189. Henningfield JE. Nicotine medications for smoking cessation. *N Engl J Med* 1995;333:1196–1203.
190. Killen JD, Fortmann SP, Kraemer HC, Varady A, Newman B. Who will relapse? Symptoms of nicotine dependence predict long-term relapse after smoking cessation. *J Consult Clin Psychol* 1992;60:797–801.
191. Killen JD, Fortmann SP. Role of nicotine dependence in smoking relapse: results from a prospective study using population-based recruitment methodology. *Int J Behav Med* 1994;1:320–334.
192. Killen JD, Fortmann SP. Craving is associated with smoking relapse: findings from three prospective studies. *Exp Clin Psychopharmacol* 1997;5:137–142.
193. Killen JD, Fortmann SP, Newman B, Varady A. Prospective study of factors influencing the development of craving associated with smoking cessation. *Psychopharmacology (Berl)* 1991;105: 191–196.
194. Fortmann SP, Killen JD. Nicotine gum and self-help behavioral treatment for smoking relapse prevention: results from a trial using population-based recruitment. *J Consult Clin Psychol* 1995; 63:460–468.
195. Hughes JR, Gulliver SB, Fenwick JW, Valliere WA, Cruser K, Pepper S, Shea P, Solomon LJ, Flynn BS. Smoking cessation among self-quitters. *Health Psychol* 1992;11:331–334.
196. Garvey AJ, Bliss RE, Hitchcock JL, Heinold JW, Rosner B. Predictors of smoking relapse among self-quitters: a report from the Normative Aging Study. *Addict Behav* 1992;17:367–377.
197. Russell MA, Merriman R, Stapleton J, Taylor W. Effect of nicotine chewing gum as an adjunct to general practitioner's advice against smoking. *Br Med J (Clin Res Ed)* 1983;287:1782–1785.
198. Sachs DP, Hodgkin JE, Bostrom AG. Improving treatment outcome in the face of increasingly severe nicotine dependence in patients seeking tobacco-dependence treatment. *Chest* 2008;134: s53002.
199. Hughes JR. The hardening hypothesis: is the ability to quit decreasing due to increasing nicotine dependence? A review and commentary. *Drug Alcohol Depend* 2011;117: 111–117.
200. Report of the Committee on Safety of Medicines Working Group on nicotine replacement therapy. Medicines and Healthcare Products Regulatory Agency (UK). 2005 [accessed 2014 May 16]. Available from: http://www.ihra.net/files/2011/07/13/MHRA_-_Report_on_Nicotine_Replacement_Therapy.pdf
201. Medicines and Healthcare products Regulatory Agency (MHRA). New advice on use of nicotine replacement therapy (NRT): wider access in at-risk populations [accessed 2015 Jul 16]. Available from: http://www.nhsgrampian.org/grampianfoi/files/IMPACT052.doc
202. Tønnesen P, Carrozzi L, Fagerström KO, Gratziou C, Jimenez-Ruiz C, Nardini S, Viegi G, Lazzaro C, Campell IA, Dagli E, *et al*. Smoking cessation in patients with respiratory diseases: a high priority, integral component of therapy. *Eur Respir J* 2007;29: 390–417.
203. Sachs D. Tobacco dependence: pathophysiology and treatment. In: Hodgkin JE, Celli BR, Connors GL, editors. Pulmonary rehabilitation: guidelines to success, 3rd ed. Philadelphia: Lippincott Williams & Wilkins, Inc; 2000. pp. 261–301.
204. Sachs D. Medical management of tobacco dependence: concepts and treatment objectives. In: Hodgkin JE, Celli BR, Connors GL, editors. Pulmonary rehabilitation: guidelines to success, 4th ed. St. Louis, MO: Mosby Elsevier; 2009. pp. 234–68.
205. Hyland A, Rezaishiraz H, Giovino G, Bauer JE, Michael Cummings K. Over-the-counter availability of nicotine replacement therapy and smoking cessation. *Nicotine Tob Res* 2005;7:547–555.
206. Benowitz NL, Zevin S, Jacob P III. Suppression of nicotine intake during ad libitum cigarette smoking by high-dose transdermal nicotine. *J Pharmacol Exp Ther* 1998;287:958–962.
207. Lemmens V, Oenema A, Knut IK, Brug J. Effectiveness of smoking cessation interventions among adults: a systematic review of reviews. *Eur J Cancer Prev* 2008;17:535–544.
208. Leone FT, Evers-Casey S. Behavioral interventions in tobacco dependence. *Prim Care* 2009;36:489–507.
209. Steinberg MB, Greenhaus S, Schmelzer AC, Bover MT, Foulds J, Hoover DR, Carson JL. Triple-combination pharmacotherapy for medically ill smokers: a randomized trial. *Ann Intern Med* 2009; 150:447–454.
210. Hays JT, Wolter TD, Eberman KM, Croghan IT, Offord KP, Hurt RD. Residential (inpatient) treatment compared with outpatient treatment for nicotine dependence. *Mayo Clin Proc* 2001;76: 124–133.
211. Hays JT, Croghan IT, Schroeder DR, Burke MV, Ebbert JO, McFadden DD, Hurt RD. Residential treatment compared with outpatient treatment for tobacco use and dependence. *Mayo Clin Proc* 2011;86:203–209.
212. Ebbert JO, Burke MV, Hays JT, Hurt RD. Combination treatment with varenicline and nicotine replacement therapy. *Nicotine Tob Res* 2009;11:572–576.
213. Ebbert JO, Croghan IT, Sood A, Schroeder DR, Hays JT, Hurt RD. Varenicline and bupropion sustained-release combination

therapy for smoking cessation. *Nicotine Tob Res* 2009;11: 234–239.
214. Abroms LC, Lee Westmaas J, Bontemps-Jones J, Ramani R, Mellerson J. A content analysis of popular smartphone apps for smoking cessation. *Am J Prev Med* 2013;45:732–736.
215. Buller DB, Borland R, Bettinghaus EP, Shane JH, Zimmerman DE. Randomized trial of a smartphone mobile application compared to text messaging to support smoking cessation. *Telemed J E Health* 2014;20:206–214.
216. Drummond MB, Upson D. Electronic cigarettes: potential harms and benefits. *Ann Am Thorac Soc* 2014;11:236–242.
217. Caponnetto P, Campagna D, Papale G, Russo C, Polosa R. The emerging phenomenon of electronic cigarettes. *Expert Rev Respir Med* 2012;6:63–74.
218. Vickerman KA, Carpenter KM, Altman T, Nash CM, Zbikowski SM. Use of electronic cigarettes among state tobacco cessation quitline callers. *Nicotine Tob Res* 2013;15:1787–1791.
219. Li J, Bullen C, Newcombe R, Walker N, Walton D. The use and acceptability of electronic cigarettes among New Zealand smokers. *N Z Med J* 2013;126:48–57.
220. Popova L, Ling PM. Perceptions of relative risk of snus and cigarettes among US smokers. *Am J Public Health* 2013;103: e21–e23.
221. Adkison SE, O'Connor RJ, Bansal-Travers M, Hyland A, Borland R, Yong H-H, Cummings KM, McNeill A, Thrasher JF, Hammond D, *et al*. Electronic nicotine delivery systems: international tobacco control four-country survey. *Am J Prev Med* 2013;44:207–215.
222. King BA, Alam S, Promoff G, Arrazola R, Dube SR. Awareness and ever-use of electronic cigarettes among U.S. adults, 2010-2011. *Nicotine Tob Res* 2013;15:1623–1627.
223. Centers for Disease Control and Prevention (CDC). Notes from the field: electronic cigarette use among middle and high school students - United States, 2011-2012. *MMWR Morb Mortal Wkly Rep* 2013;62:729–730.
224. Popova L, Ling PM. Alternative tobacco product use and smoking cessation: a national study. *Am J Public Health* 2013;103: 923–930.
225. Benowitz NL. Emerging nicotine delivery products. Implications for public health. *Ann Am Thorac Soc* 2014;11:231–235.
226. Pedersen W, von Soest T. Tobacco use among Norwegian adolescents: from cigarettes to snus. *Addiction* 2014;109: 1154–1162.
227. Post A, Gilljam H, Rosendahl I, Bremberg S, Galanti MR. Symptoms of nicotine dependence in a cohort of Swedish youths: a comparison between smokers, smokeless tobacco users and dual tobacco users. *Addiction* 2010;105: 740–746.
228. Timberlake DS, Huh J, Lakon CM. Use of propensity score matching in evaluating smokeless tobacco as a gateway to smoking. *Nicotine Tob Res* 2009;11:455–462.
229. Rapgay L, Bystrisky A. Classical mindfulness: an introduction to its theory and practice for clinical application. *Ann N Y Acad Sci* 2009;1172:148–162.
230. Elwafi HM, Witkiewitz K, Mallik S, Thornhill TA IV, Brewer JA. Mindfulness training for smoking cessation: moderation of the relationship between craving and cigarette use. *Drug Alcohol Depend* 2013;130:222–229.
231. Jain S, Shapiro SL, Swanick S, Roesch SC, Mills PJ, Bell I, Schwartz GE. A randomized controlled trial of mindfulness meditation versus relaxation training: effects on distress, positive states of mind, rumination, and distraction. *Ann Behav Med* 2007;33:11–21.
232. Brewer JA, Mallik S, Babuscio TA, Nich C, Johnson HE, Deleone CM, Minnix-Cotton CA, Byrne SA, Kober H, Weinstein AJ, *et al*. Mindfulness training for smoking cessation: results from a randomized controlled trial. *Drug Alcohol Depend* 2011;119:72–80.
233. Sachs DP, Säwe U, Leischow SJ. Effectiveness of a 16-hour transdermal nicotine patch in a medical practice setting, without intensive group counseling. *Arch Intern Med* 1993;153:1881–1890.
234. Paoletti P, Fornai E, Maggiorelli F, Puntoni R, Viegi G, Carrozzi L, Corlando A, Gustavsson G, Säwe U, Giuntini C. Importance of baseline cotinine plasma values in smoking cessation: results from a double-blind study with nicotine patch. *Eur Respir J* 1996;9:643–651.
235. Schnoll RA, Patterson F, Wileyto EP, Tyndale RF, Benowitz N, Lerman C. Nicotine metabolic rate predicts successful smoking cessation with transdermal nicotine: a validation study. *Pharmacol Biochem Behav* 2009;92:6–11.
236. Schnoll RA, Leone FT. Biomarkers to optimize the treatment of nicotine dependence. *Biomarkers Med* 2011;5: 745–761.
237. Muramoto ML, Leischow SJ, Sherrill D, Matthews E, Strayer LJ. Randomized, double-blind, placebo-controlled trial of 2 dosages of sustained-release bupropion for adolescent smoking cessation. *Arch Pediatr Adolesc Med* 2007;161:1068–1074.
238. Colby SM, Gwaltney CJ. Pharmacotherapy for adolescent smoking cessation. *JAMA* 2007;298:2182–2184.
239. Glantz SA, Barnes DE, Bero L, Hanauer P, Slade J. Looking through a keyhole at the tobacco industry: the Brown and Williamson documents. *JAMA* 1995;274:219–224.
240. American Thoracic Society. ATS policy governing relationships between the tobacco industry, ATS members, and non-members who participate in ATS activities [accessed 2014 May 23]. Available from: http://www.thoracic.org/about/governance/ethics-and-coi/resources/ats-tobacco-policy-may2013.pdf