ARTICLE TITLE: Key Issues Surrounding the Health Impacts of Electronic Nicotine Delivery Systems (ENDS) and Other Sources of Nicotine

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1. Discuss trends in the use of combustible tobacco and electronic nicotine delivery systems (ENDS).
2. Explain what ENDS are.
3. Summarize aspects of nicotine toxicology most relevant to the health implications of ENDS use.
4. Discuss current evidence regarding the potential benefits and harms associated with ENDS relative to those of combustible tobacco products and nicotine-replacement therapies.

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Key Issues Surrounding the Health Impacts of Electronic Nicotine Delivery Systems (ENDS) and Other Sources of Nicotine

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Abstract: Over the last decade, the use of electronic nicotine delivery systems (ENDS), including the electronic cigarette or e-cigarette, has grown rapidly. More youth now use ENDS than any tobacco product. This extensive research review shows that there are scientifically sound, sometimes competing arguments about ENDS that are not immediately and/or completely resolvable. However, the preponderance of the scientific evidence to date suggests that current-generation ENDS products are demonstrably less harmful than combustible tobacco products such as conventional cigarettes in several key ways, including by generating far lower levels of carcinogens and other toxic compounds than combustible products or those that contain tobacco. To place ENDS in context, the authors begin by reviewing the trends in use of major nicotine-containing products. Because nicotine is the common core—and highly addictive—constituent across all tobacco products, its toxicology is examined. With its long history as the only nicotine product widely accepted as being relatively safe, nicotine-replacement therapy (NRT) is also examined. A section is also included that examines snus, the most debated potential harm-reduction product before ENDS. Between discussions of NRT and snus, ENDS are extensively examined: what they are, knowledge about their level of “harm,” their relationship to smoking cessation, the so-called gateway effect, and dual use/poly-use.

Keywords: delivery systems, e-cigarette, electronic nicotine, harm reduction, tobacco control

Practical Implications for Continuing Education

> The use of electronic nicotine delivery systems (ENDS) has become very popular in the United States, including among youth.

> The health impacts of ENDS are only partly understood, but the preponderance of research suggests that using current-generation ENDS is significantly less harmful than using combustible tobacco products.

> Dual use of ENDS and other tobacco products is common and generates little to none of the positive health impacts of quitting combustible tobacco products altogether.

Introduction

In this review, we address the key issues around harm reduction in tobacco use, with a focus on electronic nicotine delivery systems (ENDS). Harm reduction in tobacco control is a set of concepts and strategies aimed at reducing the negative consequences and implications of tobacco use, both for individual users and for society more broadly. It does not suggest that all users will stop using tobacco products but, rather, that some users who are unable or unwilling to quit will instead switch to less harmful products, either permanently or for an interim period before stopping completely.

Harm reduction in tobacco control was a relatively minor issue mostly related to smokeless tobacco products until the introduction of ENDS in the marketplace in
the middle to late 2000s. As use of these products—the most popular to date continues to be the electronic cigarette (e-cigarette)—has become increasingly more prevalent, public health organizations must now address the central issues raised by their rapid growth in the marketplace. In brief, proponents of harm reduction using ENDS argue that these products provide significant potential for current combustible tobacco users (eg, cigarette smokers) who are having challenges quitting to switch to a product that is demonstrably less harmful. Among other concerns, skeptics and/or opponents of harm reduction argue that: 1) we do not yet know the longer-term harm of these products (or even some of the short-term-harm); 2) these products could act as a gateway—particularly for young people—to combustible product use; 3) dual use of ENDS and combustibles may inadvertently prolong combustible use; and 4) ENDS use could contribute to a renormalization of smoking.

In this review, we do not take specific policy positions or make clinical recommendations. Rather, we present the main, current, relevant research findings—at times helping to interpret the associated science—and discuss the relative strengths and weaknesses of this work, helping the reader to evaluate the existing body of evidence.

An extensive review of the research clearly shows that there are scientifically sound, sometimes competing arguments about ENDS that are not immediately and/or completely resolvable. The preponderance of the scientific evidence reviewed for this report suggests, however, that current-generation ENDS products are demonstrably less harmful than combustible tobacco products, such as conventional cigarettes, in several key ways. Although we find no evidence supporting the widely-reported claim made in a Royal College of Physicians report\(^1\) that e-cigarettes are 95% less harmful than conventional cigarettes, the assertion that current-generation versions of these products are substantially less harmful is well supported. For example, from the specific perspective of cancer, research demonstrates consistently that the use of current-generation ENDS products generates far lower levels of carcinogens and other toxic compounds (including volatile organic compounds) than combustible products.\(^2-4\)

We begin this review in the next section by presenting trends in the use of conventional cigarettes, smokeless tobacco, and ENDS. Because nicotine is the common core constituent in most of these products, and because of its addictive properties, we discuss nicotine toxicology in the second section. Our third section reviews conventional nicotine-replacement therapy (NRT), the only method of nicotine delivery widely accepted as a safe and effective tool for tobacco cessation. Sections 4 through 8 address several discrete aspects of ENDS: what they are, what we know about their level of "harm," their relationship to cessation of tobacco smoking, the so-called gateway effect, and dual use or poly-use. The ninth section considers smokeless tobacco as an important, related issue, because some of these harm-reduction issues might also apply to some smokeless products and have been raised in this context. Each section concludes with a short “Summary and Discussion” subsection offering the main take-home points. We end the review with a brief conclusion that brings together these related discussions.

Trends in Tobacco Use Across Product Types

There are several major categories of tobacco and nicotine products, with combustible products—including cigarettes, cigars, and water pipes—continuing to be the dominant category. Other important categories include smokeless products, such as chewing tobacco, snuff, or Swedish snus; ENDS (most notably, the popular e-cigarette); and NRT products, such as gum, patches, and nasal spray, used clinically for tobacco cessation.

In efforts to better understand some of the complexities of measuring trends in the use of tobacco products, we highlight some of the challenges around generating comparable measures, especially between smoking and the use of ENDS. It is essential to understand the distinctions between experimentation with and habitual use of tobacco, particularly among youth. For example, experts often use the benchmark of “100 lifetime cigarettes” to identify those who have (or had) likely moved beyond more ephemeral experimentation behaviors. For ENDS, there is not yet a similar, widely accepted measure. The absence of a reasonable dividing line may have the effect of biasing prevalence figures higher for ENDS, because it places those experimenting briefly and those using more regularly into one group.

Cigarette Use Among Adults

In recent years, the prevalence of cigarette smoking among Americans has fallen to historic lows.\(^5-8\) As Figure 1 illustrates with data from the National Health Interview Survey (NHIS), by 2015, the total number of adult smokers and

![FIGURE 1. The Decline of Cigarette Smoking in the United States (National Health Interview Survey, 1965-2015). The blue line illustrates adult prevalence (%) and corresponds to the left y-axis and the red line indicates the number of current smokers (in millions) and corresponds to the right y-axis. The x-axis indicates the year.](image-url)
the percentage of adults who smoke were both at their lowest points since the Great Depression.\(^9\)

Figure 2 presents past-month adult cigarette smoking data from both the NHIS and the National Survey on Drug Use and Health (NSDUH). In contrast to Figure 1, we separate the trends for everyday smoking and for “some-day” smoking. The largest and most dramatic trends are seen in the decreases in daily smoking. In the NHIS from 1995, past 30-day everyday smokers (Fig. 2, blue line) comprised 20.4% of the adult population, whereas by 2015, that figure had dropped to 11.7%. In the 1999 NSDUH, past 30-day everyday smokers were 21.3% of the adult population and had dropped to 13.6% by 2014 (Fig. 2, green line). In the NHIS, past 30-day some-day smokers were 4.2% of the adult population in 1995 and dropped to 3.2% by 2015. In the NSDUH, past 30-day some-day smokers were 5.4% of the adult population in 1995, and this rose to 7.3% for some-day smokers by 2015.

However, it is important to note that the number of American adults (including active military and institutionalized individuals) who currently smoke cigarettes is still approximately 40 million.\(^6\) Tobacco-control efforts deserve substantial credit for preventing the early deaths of some 8 million Americans.\(^10,11\) Despite these accomplishments, tobacco use still kills one-half million Americans each year, making it the largest preventable cause of death in the United States.\(^12\) Because smoking has a strong, negative correlation with socioeconomic status, the behavior, and its toll, are central to the challenges around health disparities in this country.\(^13\) The most recent sizeable declines in cigarette smoking in 2014 and 2015 have generated great consideration in the public health community, not only because of their magnitude but also because there are many possible ways to explain them.\(^6,7\)

**Cigarette Use Among Youth**

For public health proponents, the dramatic decline in cigarette smoking among youth in the United States, as demonstrated by numerous surveys, including the National Youth Tobacco Survey (NYTS), the National Survey on Drug Use and Health (NSDUH), and the Monitoring the Future Survey (MTF), has been a cause for celebration. Although these surveys measure the prevalence of cigarette use among youth in different ways, which has led them to produce different point estimates of use, their trends all point in the same direction: a consistent, significant, and long-term decline in youth cigarette smoking over the last 20 years. The different measures for youth smoking represent slightly different phenomena. “Ever smoking” is simply a measure of whether an individual has tried smoking at any point and does not differentiate between those who are currently smoking and those who did so in the past. Measures of “ever smoking” are typically those with the highest proportions. Some surveys ask whether an individual smoked in the last 30 days. On its own, this measure does not permit making a distinction between habitual use and experimentation; it also does not measure intensity or frequency. Sometimes, this measure is combined with another query about lifetime smoking (usually 100 cigarettes), which helps to determine whether an individual is just experimenting. Most surveys will also measure prevalence of daily smoking, which is typically lower than other measures. Some surveys also inquire more systematically about smoking frequency (eg, how many days per week or month do you smoke?) and/or intensity (eg, how many cigarettes do you typically smoke per unit of time, etc). It is important to note differences in the ages of those surveyed. For example, the NYTS surveys high school students, the NSDUH reports on youth ages 12 to 17 years, whereas the MTF survey focuses on 8th-, 10th-, and 12th-grade students.

The trends from the NYTS demonstrate substantial decreases in youth smoking regardless of the measure. The proportion of students ages 12 to 18 years who smoked cigarettes in the past month (and smoked 100 cigarettes in their lifetime) fell from 11.9% in 2000 to 2.6% in 2015. Figure 3 breaks this trend down by everyday and some-day...
smokers: the proportion of students ages 12 to 18 years who smoked cigarettes every day (and had smoked 100 cigarettes in their lifetime) fell from 6.0% in 2000 to 1.0% in 2015, whereas the proportion of students ages 12 to 18 years who smoked cigarettes some days in the past month (and had smoked 100 cigarettes in their lifetime) fell from 5.8% in 2000 to 1.5% in 2015. More broadly, the 2000 NYTS found that 28.0% of high school students had smoked cigarettes in the past month (making no distinction among everyday, some-day, and total lifetime use), a figure that fell to 9.3% of high school students by 2015.14

The NSDUH findings are similar to those of the NYTS. The proportion of youth ages 12 to 17 years who had ever smoked a cigarette fell from 34.5% in 2000 to 14.4% in 2014, whereas past-month cigarette use also fell from 13.4% to 5.0% over the same period. Similarly, youth (ages 12-17 years) who smoke cigarettes every day and at least 100 cigarettes in their lifetime has fallen from 4.2% in 2000 to 1.2% in 2014. Similarly, the MTF survey found that past-month cigarette use among 12th graders fell to 10.5% in 2016, down from 31.4% in 2000 and from a peak of 36.5% in 1997. The MTF survey also finds that 13.0% of adults smoked cigarettes every day, whereas 3.9% smoked cigarettes only on some days. In short, although the proportion of adults using e-cigarettes has grown over the last few years, daily e-cigarette use is currently less common among this population than daily cigarette use among the population of cigarette users. The reasons behind this phenomenon need to be explored further; however, currently it seems very likely that e-cigarettes are being used differently than cigarettes by many users. It remains to be seen whether this has positive or negative implications for public health.

Public health professionals have raised concerns about “poly-use”: the use of both e-cigarettes and other tobacco products, especially combustibles such as cigarettes. Accordingly, we present recent data from the Population Assessment of Tobacco and Health (PATH) study to examine poly-use. Among current (everyday and some-day) cigarette smokers in 2014, 2.6% used e-cigarettes every day, 5.6% used e-cigarettes some days, and 13.1% reported to be currently experimenting with e-cigarette use. In addition, 39.9% of current cigarette smokers reported that they had never used e-cigarettes, while 38.8% had previously used
e-cigarettes but were not doing so currently. Among current (everyday and some-day) e-cigarette users in 2014, 46.8% smoked cigarettes every day, and 15.5% smoked cigarettes some days. Furthermore, 9.4% reported that they ceased smoking more than a year ago, and another 15.4% reported that they gave up smoking in the previous year. Of these cigarette quitters, the average time since they last smoked a cigarette was 6.6 months (median, 6 months; 25th percentile, 2 months; 75th percentile, 10 months). Finally, 13.0% of current e-cigarette users reported that they had never been cigarette smokers. We discuss the complexities of dual use or poly-use below.

E-Cigarette Use Among Youth

Although sales of e-cigarettes to youth have been prohibited in most US states in the last few years (with considerable variation in these regulations across states), and, as of August 2016, federal regulations prohibit sales to those under 18 years of age, there are more epidemiologic data available on youth e-cigarette use than on adult e-cigarette use. To begin, the NYTS cited above is the longest running, nationally representative source of e-cigarette use data, and its results demonstrate the trajectory of growing e-cigarette use among students. In 2011, just 1.5% of high school students had used an e-cigarette in the past month. That figure had risen to 16.0% of high school students in 2015, before declining to 11.3% in 2016.16

The 2015 NYTS was the first year to examine daily e-cigarette use among youth. It found that 1.1% of students ages 12 to 18 years reported using e-cigarettes every day for the past month. Similarly, 1.0% of students ages 12 to 18 years reported using e-cigarettes every day and had done so for longer than the past month. Notably, this proportion of daily users is similar to the number of students who report smoking cigarettes every day. The NYTS also examines poly-use and reports that 14.0% of students ages 12 to 18 years who are everyday cigarette smokers use e-cigarettes every day, whereas 14.5% of students ages 12 to 18 years who are everyday e-cigarette users smoke conventional cigarettes every day. Thus, as of 2015, the users of the 2 different categories of products appear to be mostly different populations. Figure 4 illustrates that approximately 98% of students ages 12 to 18 years neither use e-cigarettes everyday nor smoke conventional cigarettes every day. Furthermore, among those who do use one of these products every day, dual use is not common.

Notably, other studies of youth tobacco use patterns, such as the US Food and Drug Administration (FDA) PATH study, indicate that most youths do not use e-cigarettes daily or close to daily. The Wave 1 PATH youth data report that, among youth who have ever tried an e-cigarette, 88.2% have not tried one in the last month. Of those who have ever tried an e-cigarette, just 0.2% claim to use an e-cigarette every day. The modal user used e-cigarettes just 1 day in the past month (although this was just 1.0% of ever users). Results based on a second wave of the PATH study were presented by the program’s principal researchers at the 2017 annual meetings of the Society for Nicotine and Tobacco Research and the National Conference on Tobacco or Health, allowing us to follow individuals longitudinally. Wave 2 PATH data, collected approximately 1 year after Wave 1, provide more insight into transitions into e-cigarette use and smoking. Among “never tobacco users” at Wave 1, 2.2% of youth (ages 12-17 years) and 2.1% of young adults (ages 18-24 years) reported past-30-day e-cigarette use at Wave 2.17

In 2015, the MTF survey found that 16.3% of 12th graders were using e-cigarettes each month, although notably, in 2016, this number fell to 12.5%. Although this latest finding might not indicate a new downward trend, it is the first decrease in a few years. The MTF survey is particularly useful, because it examines the phenomenon...
of flavors in ENDS products. It is possible that the novelty of e-cigarettes and the numerous flavors with youth-targeted appeal are helping to drive use among youth. The survey asked students what they were “vaping,” finding that approximately two-thirds of youth vaped “just flavoring,” and only about one-fifth knowingly vaped nicotine during their most recent use. NYTS asks a slightly different question, finding that approximately one-third of youth have “ever used an electronic cigarette device for any other substance other than for nicotine,” but it is not clear whether a respondent who was only vaping flavoring and solvent would consider that to be a “substance” in this context. Importantly, there are several limitations to the finding that the preponderance of liquids do not contain nicotine. First, a few peer-reviewed studies indicate that some ENDS products do not have accurate labeling—specifically, some products labeled as non-nicotine in fact had nicotine, although, in documented cases, these levels have typically been very low. Second, it is also possible that some respondents simply did not know what was in the liquid they were aerosolizing, although that dynamic could just as easily cut both ways in terms of the accuracy of their reporting (they reported one—nicotine vs non-nicotine—while it was actually the other). Finally, it is also possible that respondents choose not to answer truthfully, but it is difficult to identify a priori why a respondent would be motivated to do so.

In any case, the MTF survey results suggest that e-cigarette prevalence cannot be naively added to cigarette prevalence to yield a total nicotine use prevalence, because many e-cigarette users are not using ENDS with nicotine. The increase in ENDS experimentation has not yet coincided with an uptick in cigarette use in the same population. Nevertheless, some in the public health community fear that experimentation with nicotine-containing ENDS could lure some otherwise would-be nonsmokers to try using combustible cigarettes to get their nicotine dose. Examination of whether e-cigarettes are truly a gateway product into combustible tobacco use must continue, particularly as large cigarette manufacturers move deeper into the e-cigarette markets. These companies have an incentive to maintain and increase tobacco cigarettes sales, potentially by facilitating gateway use from e-cigarettes to tobacco cigarettes.

Use of Other Tobacco Products Among Adults

The primary tobacco products of concern to health organizations beyond cigarettes and e-cigarettes largely fall into a few groups: cigars (and their derivatives), pipe tobacco, and smokeless tobacco. Far more men than women use cigars and smokeless tobacco. Cigar use is more common among African American men than among non-Hispanic white men, while non–Hispanic white men use smokeless tobacco significantly more than other groups both occasionally and regularly. Although smokeless tobacco use declined among men from 1980 through 2000—dropping to near 4%—its popularity, possibly because of the proliferation of smoke-free policies and the encouragement from tobacco companies that cigarette smokers use smokeless tobacco where they cannot smoke, has rebounded somewhat since 1980s levels, such that 7.1% of adult men currently used smokeless tobacco in 2014. There is variation in the use trends of various smokeless products. For example, chewing tobacco is trending down, whereas snuff use is increasing. There is also regional variation—for example, in Wyoming, with the highest prevalence, it is 8.8%, whereas in Delaware, Hawaii, and Massachusetts, it is 1.5%. Smokeless tobacco use remains very rare among women in the United States at 0.3%.

Use of Other Tobacco Products Among Youth

The declines in the use of cigars and smokeless tobacco products among youth have been small, as reported in the NYTS. In 2009, 6.7% of high school students had used smokeless tobacco in the past month, whereas in 2015, that figure had only fallen to 6.0%, a statistically nonsignificant change. In 2009, 10.9% of high school students had smoked cigars in the past month, whereas, in 2015, 8.6% had smoked cigars. These are not the same sort of large improvements seen with youth cigarette smoking figures. Notably, cigars and smokeless tobacco are not subject to the same flavoring bans that apply to cigarettes in the United States under the FDA. This dynamic might help to explain why cigar and smokeless tobacco use have not decreased much since passage of the Family Smoking Prevention and Tobacco Control Act of 2009.

Many tobacco-control advocates argue that the relatively lax regulatory regime around noncigarette tobacco products, relative to cigarettes, contributes to the lack of a significant decline in the use of these products among young people. Determining whether these regulatory differences are driving these trends is beyond the scope of this discussion, but we should note the features of these products that might make them more attractive to youth than cigarettes. For example, establishments that offer hookah, or water pipe, tobacco (see below) are exempted from indoor smoking bans in many jurisdictions, and this tobacco is also sold in a wide array of fruit and candy flavors. Perhaps consequently, past month use of a hookah by high school students has risen from 4.1% in 2011 to 7.2% in 2015. Note that the CDC changed the response order in the NYTS questionnaire, and hookah moved from fourth or fifth in the 2011 through 2013 surveys to first—a change that also might be positively affecting this increase (newer surveys will shed
more light on this trend). The CDC returned hookah to the fourth position in 2015. Figure 5 contrasts trends across major tobacco products for US high school students.

**Summary and Discussion: Trends in Tobacco Use**

The increase in uptake of ENDS has been dramatic, including among youth. ENDS use among youth is now far more popular than any tobacco product category, although some of that use appears to be non-nicotine. At the same time, cigarette use is declining among all groups, but particularly among young people. It is possible that these trends are related—more young people are using ENDS and are not using combustibles. The evidence thus far is very mixed on what behaviors the new, young ENDS users are exhibiting after initiation (ie, what proportion are experimenting, are using occasionally [more recreationally], or are addicted), although the most recent National Institutes of Health and FDA data demonstrate that the vast majority of youth-aged ENDS users are not daily users.

**Nicotine**

Although nicotine is the primary physiological basis of addiction to tobacco and tobacco-derived products, a common misperception among much of the general public (eg, see Wilson et al24), and even among those in the public-health and health-practitioner communities,25 is that nicotine is the major cause of cancer and other diseases associated with tobacco use. Nicotine is not harmless; however, by far the most serious health risks associated with smoking are caused by the chemicals formed when the tobacco is combusted. Tobacco smoke contains some 7000 chemicals, and hundreds of them are toxic and/or carcinogenic. It is the inhalation of “tar” particles and toxic gases into the smoker’s lungs and, similarly, nonsmokers’ exposure to second-hand smoke, that result in the vast majority of the death and disease attributable to active and passive smoking.26-30

The 2014 US Surgeon General’s Report reviews the scientific literature on nicotine toxicity and concludes that the evidence is sufficient to conclude that:

- At high enough doses, nicotine has acute toxicity;
- Nicotine activates multiple biological pathways through which smoking increases the risk for disease;
- Nicotine exposure during fetal development, which is a critical window for brain development, has lasting, adverse consequences for brain development; and
- Nicotine adversely affects maternal and fetal health during pregnancy, contributing to multiple adverse outcomes, such as preterm delivery and stillbirth.

The Surgeon General also indicates that the evidence is suggestive (but insufficient to conclude) that nicotine exposure negatively impacts the developing brain of adolescents.

The scientific evidence is inadequate to conclude the presence or absence of a causal relationship between exposure to nicotine and the risk of oral, esophageal, and pancreatic cancer.12 However, the Surgeon General points out that those who smoke have a higher risk of developing these cancers than those who use smokeless tobacco, although exposure to nicotine is similar for both. This suggests either that other substances underlie the differential risk of developing these cancers and/or that we do not sufficiently understand the causal pathways. The pathway to nicotine exposure may also be an explanatory factor: ingestion through the oral mucosa for smokeless tobacco users compared with inhalation into the lungs by smokers.31

Exposure to nicotine has negative health implications for pregnant women and fetuses, including the possibilities of...
low birth weight, premature birth, stillbirth, miscarriage, fetal neurotoxicity, and fetal lung development challenges.\textsuperscript{31,32} Nicotine is also suspected of contributing to delayed wound healing, peptic ulcer disease, esophageal reflux, and atherosclerosis, although it does not appear to enhance thrombosis in humans.\textsuperscript{33} Nicotine has also been linked to lung inflammation in adults, possibly through its chemotactic effects, which in turn contribute to chronic obstructive lung disease.\textsuperscript{32}

Cigarette smoking delivers nicotine much faster than other nicotine-delivery methods, and slower delivery of nicotine may be less harmful. Faster nicotine delivery results in a higher concentration of nicotine in arterial blood and intensifies the stimulation of the cardiovascular system. Clinical studies of pipe smokers and users of the transdermal patch suggest that substances other than nicotine trigger the acute cardiovascular events associated with cigarette smoking. However, more testing is needed to definitively determine this.\textsuperscript{32,33} Several studies have examined the health effects of long-term use of Swedish-style snus, a form of high-nicotine snuff.\textsuperscript{34,35} A meta-analysis of these studies found no association with cardiovascular disease,\textsuperscript{35} suggesting that nicotine alone does not cause a significant increase in heart disease, at least not from this method of delivery.

**Summary and Discussion: Nicotine**

Although nicotine can be toxic, the overall scientific consensus is that the vast proportion of harm from tobacco comes from substances produced by combustion. Thus, the largest harm of nicotine comes from its addictive properties, which trap people into using combustible tobacco products. That said, there is evidence that nicotine (in any form) has negative cardiovascular effects and is harmful for fetal development and possibly for adolescent brain development. The link thus far to cancer is comparatively weak, although new evidence suggests that it may have a small-to-modest effect on a few cancers, particularly in terms of tumor onset and growth.

**NRT and Other FDA-Approved Medications for Smoking Cessation**

NRT first entered the marketplace in the 1970s to help smokers quit, and it has been a mainstay of clinical practice-recommended cessation treatment since that time. Before the advent of ENDS, many scholars had suggested liberalizing the regulatory approach to NRT to facilitate long-term NRT use as a harm-reduction strategy.\textsuperscript{36} Five types of NRT (gum, patch, lozenge, inhaler, and nasal spray) have been approved by the FDA as safe and effective medications for tobacco cessation. NRT was initially available to smokers only by prescription,\textsuperscript{37} but, since 1996, 3 forms of NRT (patch, lozenge, and gum) have been available over the counter.\textsuperscript{38} In addition to NRT, 2 non-nicotine prescription medications, varenicline and bupropion, have been approved by the FDA as safe and effective treatments for tobacco dependence.\textsuperscript{39}

Designed to satisfy tobacco users’ physiologic dependence on nicotine, including cravings, NRT thereby eases the process of quitting tobacco use. Research suggests that NRT increases the chances of quitting by 50% to 70% regardless of whether additional behavioral cessation support (counseling) is provided, although some more recent findings call the efficacy of NRT alone into question.\textsuperscript{40} With counseling, the effects of NRT are boosted.\textsuperscript{41} There is little evidence that any single type of NRT is more effective than another.\textsuperscript{42,43} However, it has been demonstrated that combination NRT (the patch plus an “as-needed,” more immediate release form of NRT, such as the mini-lozenge or gum), is more effective than the patch alone.\textsuperscript{42,44,45} One meta-analysis of sex differences in NRT efficacy suggested that men may benefit more than women from NRT, particularly over the longer term, in the absence of additional nonpharmacological cessation support.\textsuperscript{46}

Clinical trials and observational studies demonstrate that NRT is much safer than combustible tobacco. Evidence in human trials suggests that NRT is not carcinogenic and does not cause clinical lung or heart disease. For smokers who have cardiovascular disease, studies have found that it is much more dangerous to continue smoking than to use NRT. For pregnant women; however, evidence on the use of NRT during pregnancy is insufficient to conclude that it is safe for them to use.\textsuperscript{44} Evidence on the safety of long-term NRT use is lacking but, according to the Royal College of Physicians (RCP), “there are no grounds to suspect appreciable long-term adverse effects on health.”\textsuperscript{28}

Despite its effectiveness for supporting quit attempts and its positive safety profile, there are some disadvantages associated with NRT. All forms of NRT deliver nicotine to the brain more slowly than smoking, so users may resort to dual use of NRT and cigarettes to satisfy their cravings, particularly if they are heavy smokers. Moreover, smokers are often not well informed about proper NRT use and typically underdose themselves when using NRT for smoking cessation, resulting in a chronic state of low-level nicotine withdrawal. In addition, recent research suggests that some consumers falsely believe NRTs are no safer than cigarettes because they contain nicotine; therefore they may not use NRT in optimal doses or long enough to reap the full benefits.\textsuperscript{47}

Under current US law, NRTs are regulated as drugs, devices, or combination products by the FDA and thus must meet a safety and effectiveness standard. Tobacco products, in contrast, are regulated using a public health
standard that takes into account both users and nonusers of the product. Because NRTs are marketed, packaged, and promoted only as cessation treatments, their potential for wider product appeal and reach may be hindered. Moreover, those wishing to quit or reduce their tobacco use, particularly less affluent consumers, may be inhibited from purchasing these products because of cost constraints. Cigarettes are almost universally more readily available at point-of-sale in a wide range of retail settings, whereas NRTs are not. Many proponents of NRTs argue that onerous regulations have discouraged innovation and, as a result, the development of new pharmaceutical nicotine-replacement products has stalled. Finally, the FDA does not permit long-term use of tobacco-cessation medications, and thus prescriptions for these medications are usually limited to 2 to 6 months. As a result, individuals trying to quit may lose insurance coverage for these medications while still experiencing tobacco withdrawal; the only option for them is to purchase over-the-counter NRT out-of-pocket or return to combustible use—clearly the least healthy option.

NRTs have not proven to be a universal remedy for ensuring long-term smoking cessation. Sustained quit rates on NRT and non-nicotine FDA-approved smoking cessation treatments (bupropion and varenicline) have ranged from approximately 10% to 30%. Estimates suggest that about 70% of the approximately 40 million adult smokers in the United States want to quit, but only approximately 5% of those who make a quit attempt succeed in a given year—in part because most of them try to quit on their own without counseling or FDA-approved medication support. One reason may be that NRT and non-NRT cessation medications are not marketed as attractive long-term alternatives to tobacco, in part because government regulators have concerns that long-term use will promote medication dependence. Moreover, because NRTs have limited product appeal to consumers, they have not proven to be strong substitutes for tobacco products.

Summary and Discussion: NRT and Other FDA-Approved Medications for Smoking Cessation

There is consensus that NRT and non-nicotine FDA-approved medications for smoking cessation are safe and effective. There is evidence that if used properly, these medications increase the likelihood of successful quitting. There is also evidence that many users do not use these medications effectively or as recommended. There are also issues surrounding access (including the requirement of a prescription, in some instances, and cost), limiting their availability to those who could benefit from them. Access challenges also include limited insurance coverage and the FDA's objection to long-term NRT use (under the logic that they do not want to promote nicotine addiction)—in such cases, many individuals addicted to tobacco are returning to combustible tobacco use when NRTs and non-nicotine medications could aid them in cessation and prevent their return to combustible tobacco use.

What Are ENDS?

The terms “ENDS” and “e-cigarettes” tend to be used interchangeably; however, there are many different types of ENDS available to consumers, with e-cigarettes being the most common. Invention of the modern e-cigarette is credited to a Chinese pharmacist, Hon Lik, who patented his device in 2003. ENDS can resemble not only conventional tobacco products such as cigarettes and cigars but also everyday items such as USB flash drives or pens. Most ENDS consist of a rechargeable, battery-operated heating element and a replaceable or refillable cartridge for the e-liquid. An atomizer heats the liquid in the cartridge to convert it into an aerosol, which is then inhaled by the user. Most of these products are rechargeable, but some are disposable.

There have already been several generations of ENDS. Rechargeable and disposable e-cigarettes are referred to as first-generation ENDS. Tank systems, developed mostly by smaller independent manufacturers, are considered second-generation products. Some studies suggest that these newer products deliver nicotine more efficiently or at higher levels than many of the first-generation products. Many experienced ENDS users report preferring these devices. Personal “vaporizers” are third-generation ENDS, which are typically sold in so-called “vape” shops. These devices allow users to have more control over the liquid flavors, nicotine, and chemicals used. Fourth-generation delivery devices with digital displays are also now available in the marketplace, although there is little research on these devices.

There are also related products entering the marketplace. One major product receiving attention is the “heat-not-burn” product from Philip Morris International (PMI) (New York, NY) called “IQOS” that heats tobacco but does not combust. There is little research on what substances are released after the device heats the tobacco-based paste. The physical effects on users are also not yet known.

Unlike the new “heat-not-burn” products, ENDS do not contain actual tobacco leaf, although ENDS liquids with nicotine are derived from tobacco, and the aerosol exhaled resembles tobacco smoke. These products vary considerably in their ingredients and ability to deliver nicotine. Some liquids used in some ENDS products do not contain any nicotine at all. Propylene glycol and glycerin are primarily used to create the aerosol that is emitted when mixed with water. Various additives are common, including sugars, ethyl alcohol, non-nicotine pharmacologically active compounds, and stabilizers. In addition, as of 2014, there were
more than 7700 e-cigarette flavors available, and it is likely that there are many more available today.\textsuperscript{57}

In the past decade, we have witnessed a proliferation of ENDS. The marketplace is vast: during 2013 through 2014, there were an estimated 466 brands available for sale, and consumers spent approximately $3 billion on ENDS products globally.\textsuperscript{57,58} These numbers have almost certainly grown since then, and although reliable recent data are sparse, the most recent market forecasts predict that global sales will rise to more than $10 billion in 2017,\textsuperscript{59,60} including a 2017 estimate of $4.4 billion in the US market alone.\textsuperscript{61} Notwithstanding the fairly dramatic emergence of these new products, however, ENDS currently account for less than 5% of the US tobacco market.\textsuperscript{62} Some forecasts suggest that ENDS sales will rise to $50 billion by the year 2030, and the future of these products will be strongly determined by competition in the marketplace among ENDS manufacturers; however, because it is a new marketplace, it is very difficult to predict.\textsuperscript{58}

The ENDS marketplace is evolving rapidly in terms of the types of firms involved. Small companies initially dominated the ENDS market, and these firms had no links to the tobacco industry. Today, however, all transnational tobacco companies sell these products. Increased concentration of the ENDS market in the hands of the transnational tobacco companies is concerning to the public health community, given the industry’s legacy of obfuscating many fundamental truths about their products and misleading the public with false claims, including that low-tar and so-called “light” cigarettes would reduce the harms associated with smoking. Although industry representatives are claiming interest in ENDS because of their harm-reduction potential, many observers believe that profit remains the dominant motivation. Recent activities—including large research and development expenditures on ENDS product development—by the large tobacco multinationals demonstrate that they almost certainly have strategies already in place not only to participate in this new market but quite possibly to dominate it. To gain insight into these developments, it is crucial to carefully monitor the entire marketplace of nicotine products, including sales trends, new products, and firms’ efforts to situate themselves in new ways (eg, seeking a modified risk designation for a product).

At least one major tobacco company is ostensibly addressing the issue of harm reduction in their US business strategy. For a couple of years, PMI has been heavily promoting its new heat-not-burn tobacco product, IQOS, in Europe and Asia. They have reported that they are examining the level of potential harm and claim in their promotional materials that it emits lower levels of harmful substances than combusted tobacco products.\textsuperscript{63} Importantly, there has been little independent research on the harm profile of this product to date, so it is not yet possible to compare it with other products about which we know more, including combustibles and ENDS. In December 2016, PMI filed a Modified Risk Tobacco Product (MRTP) application with the FDA. Notably, to date, the FDA has yet to accept the claims in any such application. PMI filed a Premarket Tobacco Product Application to commercialize IQOS on March 31, 2017 (all novel tobacco products require this). Note that any product making actual cessation claims will need to be regulated as a drug under the FDA’s Center for Drug Evaluation and Research, and not the agency’s Center for Tobacco Products, which regulates tobacco products that do not make cessation claims.

**Summary and Discussion: What Are ENDS?**

The products that we call ENDS are a rapidly evolving and broad set of increasingly popular products. Some devices deliver nicotine, whereas others do not (we do not know the proportions, although recent research\textsuperscript{18,19} suggests that they are significant). There are many different types of firms in the marketplace, but the large tobacco multinationals increasingly are acquiring market share. The incentives are likely mixed, depending on the firms (eg, to create a less harmful product), but it is clear that the established, large firms are positioning themselves to dominate any likely development.

**ENDS and Levels of Harm**

Despite a lack of definitive evidence, there is growing consensus from the available research that use by adults of current-generation ENDS is likely to be less harmful than smoking conventional cigarettes or other combusted tobacco products.\textsuperscript{1,58} The continuation of this consensus is potentially undercut by a lack of regulation or product standards, which could lead to more harmful and/or substandard products. At this time, however, ENDS contain and produce substantially lower levels of toxicants than combustible tobacco products.\textsuperscript{1,64} Passive ENDS use may still elevate nicotine levels of bystanders from exhaled aerosol—exhaled e-cigarette aerosol reportedly elevates serum cotinine levels of bystanders from exhaled tobacco.\textsuperscript{65} ENDS aerosol does not deliver high levels of carbon monoxide, another favorable characteristic compared with combustible tobacco.\textsuperscript{1} The exact amount of harm and/or risk reduction for those who use ENDS or are exposed to ENDS aerosol is a topic of vigorous, ongoing debate.

There are some important caveats to consider in terms of the risk and harm profiles. First, there is enormous heterogeneity in the ENDS marketplace, and there is no guarantee that new products (and perhaps some existing ones)—particularly in a policy environment with little or no regulation—will be substantially less harmful than combustibles.
Tobacco Control in the Era of ENDS

A logical remedy to such a challenge would be stronger effective regulation and monitoring, a topic beyond the pur-view of this discussion.

A related concern is that much of the business model of ENDS firms is predicated upon their products’ delivery of nicotine and its addictive nature. Manufacturers are experimenting with this element of these products, and some of the components identified as affecting a device’s ability to deliver nicotine to the user—including the size of the droplets and the heat at which the e-liquid enters the lungs—may prove to be those that most affect the level of harm.

The vast preponderance of the existing scientific evidence suggests that the levels of carcinogens and other toxicants delivered to users of current-generation ENDS are substantially less than those delivered by combustible tobacco. A 2016 report published by the RCP in the United Kingdom asserts that, although ENDS have not been in use long enough to be absolutely certain about their harm profile, the available evidence suggests that mouth and throat irritation are the main health issues experienced by users in the short term (see also Hajek et al). The levels of tobacco-specific nitrosamines (TSNAs) and other carcinogens in ENDS aerosol are much lower than those found in tobacco smoke, decreasing the risks of developing cancer over the longer term, according to the RCP report. The report argues that the level of toxins, rather than their presence, is the most important determinant of how harmful a product is to humans. After reviewing and studying all available evidence to date, a main conclusion drawn in the report is that, “[a]lthough it is not possible to precisely quantify the long-term health risks associated with e-cigarettes, the available data suggest that they are unlikely to exceed 5% of those associated with smoked tobacco products, and may well be substantially lower than this figure.”

The RCP report’s controversial quantification of relative harm centers on an estimate produced originally by an expert panel convened by the Independent Scientific Committee on Drugs. Public Health England has also endorsed the same estimate. However, the validity of the estimate that e-cigarettes are approximately 95% less harmful than conventional cigarettes has been strongly criticized by many, including in an editorial in The Lancet, in which it was characterized as careless and having insufficient scientific basis. The estimate of the Independent Scientific Committee on Drugs does not appear to have been calculated from any known toxicological, epidemiological, or other empirical data but, rather, represented the opinion of the committee.

The 2016 Surgeon General’s Report on e-cigarette use among youth and young adults did not attempt to quantify the harm of e-cigarette relative to tobacco cigarettes. The report’s conclusion about harms emphasized both the reduction on toxicants relative to tobacco cigarettes and the uncertainties associated with the absolute level of harm.

Notably, the peer-reviewed research from the 2 or 3 years of scholarship before these reports is mixed in its findings and conclusions. In a systematic review of ENDS research, Pisinger and Dosing were unable to draw definitive conclusions about the harm profile of these products because of the limited number and often poor quality of the studies reviewed. Results among studies were often inconsistent and contradictory. Of additional concern was that almost one-third of the 76 studies included in the review were funded or supported by ENDS manufacturers, creating an enormous potential for conflict of interest. Overall, however, the reviewers reported that the evidence consistently confirmed the presence of toxic substances (ie, fine/ultrafine particles, cytotoxicity, various metals, TSNAs, and carbonyls), but at levels much lower than those found in conventional, combustible cigarettes.

Another major review focused more on the short-term and longer term effects. In 44 studies reviewed, the author reported that it is highly likely that ENDS aerosol contains fewer toxic substances than tobacco smoke; however, because of the limited available research on both short-term and long-term effects, the author could not conclude definitively that ENDS are less harmful than conventional cigarettes. The author also highlighted the need for more research on the impact of second-hand and third-hand aerosol exposure.

A 2014 review of chemical analyses of ENDS products found enormous heterogeneity, with toxic chemicals and carcinogens present in refill solutions, cartridges, aerosols, and aerosol emissions of e-cigarettes. Many of the products evaluated in the review were not available for sale in the United States, and there was considerable variation in the levels of nicotine, TSNAs, aldehydes, metals, and volatile organic compounds and in flavors, solvent carriers, and tobacco across different products.

Some studies have focused on the nature and effects of the ENDS aerosol. Notably, it is not merely water vapor, as is frequently claimed in the marketing for these products. Burstyn reviewed the scientific literature on the chemistry of ENDS aerosols and liquids to compare users’ exposure to ENDS aerosol in relation to occupational safety standards. The author concluded that, in normal conditions of ENDS use, the levels of toxicants inhaled are likely far below the recommended thresholds for occupational exposure. Farsalinos et al observed that similar levels of TSNAs were present in e-liquids before aerosolization and in the aerosol generated after the e-liquids were heated by ENDS. However, that study could not detect whether the source of TSNAs in the aerosol was the e-liquid on its own, or
whether the heating of the ENDS produced additional TSNAs. The aerosol emitted by ENDS is not harmless, but Saffari et al\(^76\) reported that second-hand exposure to metals and organic compounds in ENDS emissions was markedly lower than exposure to conventional second-hand smoke.

Potential health risks may occur from toxicants produced during the vaporization process, when the propylene glycol or glycerin used to create the aerosol is heated.\(^1\) In a controversial study, Jensen et al\(^77\) used nuclear magnetic resonance spectroscopy to test the degradation products from an e-cigarette tank system when the e-liquid was vaporized at high temperature. The results suggested that e-cigarette use presents an elevated risk of exposure to formaldehyde. Some experts contend that this methodology was fundamentally flawed. E-cigarette users would not heat the e-liquids at such high temperatures, because doing so would make the aerosol take on an unpleasant taste.\(^78,79\)

Farsalinos et al\(^78\) conducted a similar study and concluded that high levels of aldehydes are produced only in atypical situations when the e-liquid overheats. In such situations, and in agreement with the argument made above, the e-cigarette user would avoid using the device because the overheated liquid would produce an unpleasant taste. Those authors concluded that the levels of aldehydes produced under normal conditions of ENDS use are negligible.

In addition to the vaporized liquid, ENDS devices include metals, ceramics, and rubber, which may become aerosolized upon heating. Particles of copper, nickel, and silver have been found in ENDS aerosol at higher levels than in tobacco smoke. It remains to be determined whether these particles represent a significant potential for harm to users.\(^1\)

The flavorings used in e-liquids have raised safety concerns. Inhalation by long-term users of ENDS products generating aerosol that contains heated flavors may be associated with inflammation of the lung and airways.\(^1,80\)

Some ENDS products contain nicotine and thus present a potential hazard to adolescent brain development and fetal development.\(^58\) Concerns have been raised about the potential for nicotine poisoning of children, which can be lethal if ingested in high enough doses.\(^81\) The high nicotine concentration in e-liquids in some ENDS products can be a toxic risk for children through unintentional nicotine exposure after inhalation or ingestion.\(^82\) A 2014 review indicated that the number of calls to poison centers had increased after inhalation or ingestion.\(^82\) Another recent review\(^86\) relating to the cardiovascular effects of using ENDS found a paucity of published research on this topic; however, among those studies that examined such research, most demonstrated a reduced risk from ENDS use compared with traditional tobacco smoking. No studies have been published in the peer-reviewed literature regarding an association of ENDS use with thrombosis or platelet reactivity, nor have studies directly associated ENDS with atherosclerosis, although nicotine in general is suspected of causing atherosclerosis in other contexts. The authors of the review noted that it is not possible to extrapolate research findings related to the cardiovascular effects of smokeless tobacco use to ENDS use, because nicotine is delivered to ENDS users through a different mechanism.

Another recent review\(^86\) points out that the aerosols in ENDS contain carbonyls in levels that can be harmful for cardiovascular health and also deliver nicotine, which can increase the risk of cardiovascular disease. The author cautions that, although these products are marketed as safer alternatives to cigarettes, the evidence is currently insufficient to definitively draw that conclusion.

Carnevale et al\(^88\) compared the acute changes in vascular function resulting from traditional tobacco smoking or ENDS use among a cohort of 40 study participants who did not have cardiovascular disease. Although both products increased oxidative stress and endothelial dysfunction, the impact was less from ENDS. The authors recommend more research to fully determine the vascular effects of ENDS use, which are presently unknown.

In a study of 24 participants, Vlachopoulos et al\(^89\) observed increased aortic stiffness from a 30-minute session of e-cigarette use, which was similar to the unfavorable effects experienced after 5 minutes of tobacco smoking. The effect on arterial stiffness disappeared within 30 minutes for users, the actual occurrence of these incidents is extraordinarily rare—less than a single occurrence per million e-cigarettes sold.\(^84\) Meo and Asiri\(^83\) reviewed 28 studies and observed that e-cigarette use was associated with some gastrointestinal symptoms, including nausea and vomiting, as well as headache, dizziness, dry cough, eye irritation, and upper respiratory tract irritation.
after the discontinuation of ENDS use but persisted for 1 hour after tobacco smoking, despite the shorter exposure time compared with e-cigarette use. The study established an association between e-cigarette use and acute arterial stiffness in the short term; however, it remains to be determined whether this acute effect will result in cardiovascular disease over the longer term.

Notably, the section above on nicotine mentions that the long-term exposure to nicotine from using of Swedish-style snus has not been associated with the risk of heart disease.\textsuperscript{34,35} This suggests that, although the nicotine in e-cigarettes causes the aforementioned cardiovascular effects, these effects may not cause a significant increase in heart disease risk among users. That said, it is possible that the aerosolized nicotine delivered by ENDS may be different in this respect.

**High Temperatures**

There is a possibility that there are risks associated with ENDS use and smoking that are not associated with chemical exposure but instead are caused by unsafe temperatures of aerosol or smoke. Loomis et al\textsuperscript{90} review the evidence on the carcinogenicity of coffee and mate, finding that there is insufficient evidence to conclude that either drink is inherently carcinogenic and that coffee may even reduce the risk of some cancers. However, they report that drinking either of these at very high temperatures does appear to increase risk for esophageal cancer.

This conclusion suggests the possibility that inhalation of aerosol at high temperatures may do so as well. Current-generation ENDS aerosol would typically be inhaled at a lower temperature than tobacco cigarette smoke,\textsuperscript{78} but aerosol may still be hot enough to cause throat and lung damage along with elevated cancer risk. This concern would also apply to heat-not-burn tobacco products, including IQOS, for which PMI has an application in to the FDA as an MRTP.

**Summary and Discussion: ENDS and Levels of Harm**

The research suggests that, on some fundamental levels, using current-generation ENDS is less harmful than using combustible products. In particular, there is strong evidence that the levels of carcinogens and other toxicants are lower for the average ENDS user compared with the average combustible tobacco product user. However, the potential dangers of nicotine discussed above—particularly to fetal and adolescent brain development—still apply. Furthermore, the early evidence suggests that there is the potential for negative cardiovascular effects, an area that demands more research. Also, accidental ingestion of these liquids is clearly dangerous, which demands proper packaging of these products.

Finally, it is important to note that most of these studies are based on a limited number of products and, of course, only products now in existence. In an environment wherein ENDS-related regulation is only beginning, there is danger that existing products’ harm profiles may vary greatly or that manufacturers, if not regulated and monitored, will begin to make products that are markedly more harmful than what currently exists.

**Gateway Effects**

Some practitioners and researchers in the tobacco-control community have expressed concern that ENDS use may be a “gateway” to smoking combustible tobacco products. We are primarily concerned with youth and young adults, but there is also the possibility that ex-smokers of any age could be enticed back to nicotine use, and perhaps even all the way back to smoking. A related concern is that some youth will end up using nicotine when they would not otherwise have done so, even if they do not end up progressing to smoking combustible tobacco products. Other scholars express more skepticism about whether such effects exist or are substantial (eg, see Kołodziewski and Warner\textsuperscript{91}).

Taking the second concern first, there is the possibility that some or many youths will indeed end up trying e-cigarettes who would not otherwise have tried nicotine. Schneider and Diehl\textsuperscript{92} have identified the ways in which this might occur. Youths might be more willing to initially try e-cigarettes than cigarettes because: 1) they are enticed by the variety of flavors\textsuperscript{93}; 2) they believe that ENDS are less harmful than cigarettes\textsuperscript{94}; 3) they can more easily afford ENDS; 4) they believe that ENDS use seems “cooler” than smoking; 5) they find that ENDS use is easier to conceal at school and at home\textsuperscript{95}; and 6) they believe that ENDS use is more socially acceptable. There is evidence that items 1, 2, and 5 are true, whereas the other 3 items are quite plausible, so it is likely that some youths are using ENDS who would not otherwise smoke. However, as Miech et al\textsuperscript{18} point out, many youths who experiment with ENDS do so with non-nicotine e-liquid, so we cannot assume that ENDS users among the young population are nicotine users.

The arguably greater concern is that ENDS use represents a causal gateway to conventional combustible cigarette use. If youth ENDS use has a causal effect on youth smoking, then it is much easier to imagine that whatever broader cessation advantage that ENDS have and/or the potential reduced harm effects for those adults who switch from combustibles to ENDS could be entirely offset, and even outweighed, by increases in the youth smoking rate. Levy et al\textsuperscript{96} set up a useful framework that elucidates the causal question of interest: Are there youths who would not have become smokers who do become smokers because of their exposure to e-cigarettes? Unfortunately, it is extremely
difficult to answer this question. In fact, McNeill et al, after addressing the difficulty of isolating the true gateway effect of e-cigarette use, wrote that, “we strongly suggest that use of the gateway terminology be abandoned until it is clear how the theory can be tested in this field.”69 This is an understandable impulse; however, because this prospect of a gateway effect is so pivotal to the overall advisability of a permissive regulatory strategy toward ENDS, scholars are right to attempt to answer this question.

There are at least a few compelling reasons why it is so difficult to determine whether there is a causal gateway—even more difficult than the already challenging task of determining the causal effect of ENDS on cessation. First, it is unethical, and thus not possible, to conduct randomized controlled trials in which participants are randomly assigned to use ENDS or not to determine whether they subsequently initiate smoking. Second, we should expect significant differences in smoking propensity over time would occur, particularly in young people,97 making causal conclusions difficult if not impossible. The recent Surgeon General’s report on youth e-cigarette use has reported on several recent longitudinal studies that seek to examine this phenomenon.34 These studies typically find that a greater proportion of youth e-cigarette users subsequently try combustible products compared with individuals who have never used e-cigarettes. Notably, recent PATH data showing that approximately 30% of youths who had vaped, but had not smoked, in the past 30 days at baseline had smoked a cigarette in the past 30 days at follow-up.17 However, the Surgeon General’s report also points to the many weaknesses of these studies, including uncertain causality, limited sample sizes, short duration, and measurement issues (eg, daily smoking vs experimentation). In addition, these results are sensitive to researchers’ decisions on the inclusion or exclusion of different variables that might be considered either confounders or mediators, depending on the conceptual model being used (eg, depression, expectations of health effects, impulsivity, etc). Future research will need to address these issues. Holding this research to a certain set of standards would help to identify the studies with greater methodological validity. For example, using large, national samples is preferred (see Miech et al,98 which is the first study of this kind to use a national—although, unfortunately, not very large—sample). Also, having more than 2 points in time will help to track behavioral change better (there are no studies yet of this nature). The use of surveys that measure many confounding variables is preferable, and researchers should try using different theoretically defensible combinations of these variables in the analyses to determine the robustness of their findings. It is arguably quite likely, however, that evidence on both sides of this debate from these types of studies will simply continue to accumulate, depending in considerable part on the nature of the data, the study design, and which variables are included in the analyses.

Several recent econometric studies have used natural experiments wherein policies among different states differed to generate causal evidence on the presence of gateway effects. Because some states banned youth access to ENDS before others, it is possible to determine whether states that banned this access saw greater or lesser declines in youth smoking compared with states that did not. The advantage of this approach is that it obviates many of the specific confounding issues discussed previously. Friedman99 and Pesko et al100 examined state-level variation in ENDS minimum age requirements and found that minimum age requirements lead to more smoking. In contrast, Abouk and Adams101 observed that minimum age requirements for ENDS reduced tobacco smoking. It is possible that there are time-varying, state-level confounders that can account for these discrepancies, but it is noteworthy that some estimates actually show a negative gateway rather than a positive one. Additional weaknesses include the inability to measure de facto youth access and use in the reports by Friedman and Pesko et al.

A possible “reverse gateway” might help to explain why youth smoking has declined substantially during the period when ENDS use by youth has grown exponentially. There remains, and will remain, substantial uncertainty surrounding the true gateway effect of ENDS. If it does turn out to be the case that ENDS reduce youth smoking, the main policy significance would be that there is not a positive gateway because, realistically, it is unlikely that health practitioners or governments are going to be encouraging youth to use nicotine.

Summary and Discussion: Gateway Effects

The evidence for a gateway effect—ie, that users of ENDS become combustible tobacco products users because of trying/using ENDS—is inconclusive. Much of the challenge lies in the limited methodological tools at our disposal to answer this question effectively; it is simply not ethical to assign individuals to start ENDS use in a randomized controlled trial. Recent studies using longitudinal data have generated mixed results and were methodologically challenged. Studies using a natural experiment based on state-
level age restrictions on ENDS have also generated mixed results, and this research also faces methodological challenges. In any event, more research is needed in this area, with the important caveat that many or even most of these studies will suffer from the same inherent methodological challenges that we observe with existing research.

ENDS and Smoking Cessation

At this point, there is not conclusive evidence that demonstrates a causal effect of ENDS use on smoking cessation, in part because there has been only 10 years of experience of ENDS use in the general population. The 2 most comprehensive recent reviews are by Malas et al\textsuperscript{102} in the Journal of Nicotine and Tobacco Research and a recently updated Cochrane Review by Hartmann-Boyce et al.\textsuperscript{103} These reviews come to essentially the same conclusion, albeit with different emphasis. Malas et al judge that the cessation value of ENDS is “inconclusive” because of the limited quality of the studies performed to date. However, they go on to state that, “[w]hat limited evidence there is seems to point to e-cigarettes as potentially useful in helping some smokers quit cigarette smoking.”\textsuperscript{102} This is a somewhat more tentative conclusion than that reached by the Cochrane Review, which concludes that, “There is evidence from 2 trials that e-cigarettes help smokers to stop smoking in the long term compared with placebo e-cigarettes. However, the small number of trials, low event rates and wide confidence intervals around the estimates mean that our confidence in the result is rated ‘low’ by Grading of Recommendations, Assessment, Development and Evaluation (GRADE) standards.”\textsuperscript{103} Clearly, additional research on the effectiveness of ENDS for smoking cessation is needed.

The Cochrane Review relies heavily on the only 2 randomized controlled trials (because such studies are typically conceptualized as having the highest standard of evidence, if executed well) conducted to date, which demonstrate that ENDS have efficacy similar to that of the nicotine patch without behavioral assistance. Nicotine-containing ENDS products were slightly more effective but not statistically different from the patch, whereas those that did not contain nicotine were equally as effective as the patch. The study by Brown et al, which Malas et al rated as having the highest quality evidence, was a cross-sectional study that included a representative sample of UK smokers.\textsuperscript{104} The authors observed that quit attempts involving ENDS had a higher probability of success than those involving either NRT or no assistance.

Longitudinal studies conducted to date have been highly contradictory, perhaps owing to the difficulty in making valid inferences when there is not random assignment of participants. There are likely to be substantial differences between the sort of smokers who use ENDS and those who do not; and, although adjustment for observable differences can help to reduce bias, it cannot eliminate it completely. One particularly pernicious form of bias occurs in cohort studies that enroll smokers at baseline, assess quitting at follow-up, but only measure ENDS use at baseline. Successful ENDS quitters will be selected out of the study, because they are no longer smoking at baseline, leaving only a residual of lower probability quitters using e-cigarettes at baseline.\textsuperscript{105} A second validity concern with this design is that successful quitters who were not using ENDS at baseline may have initiated ENDS use between baseline and follow-up.

Beyond the need to assess ENDS use at both baseline and follow-up to record ENDS initiation between these time points, Malas et al call on researchers to consider variations in product type, nicotine content, user characteristics, and use patterns that can affect study results.\textsuperscript{102} Researchers should also be aware of external validity concerns, including heterogeneous effects across places, population subgroups, and device types.

A 2015 report by Public Health England argues that, because e-cigarettes appear to have more product appeal to smokers than NRT, they present an opportunity to interest more smokers in quitting.\textsuperscript{69} Appeal is a critical concept, because even the most efficacious cessation methods will not substantially improve population health if smokers are not interested in using them. The unique appeal of e-cigarettes to smokers is critical to understanding their potential to reduce smoking rates. The other side of this scenario is the potential of appealing products to entice never-smokers or ex-smokers into nicotine use. Finally, there is the substantial concern of “dual-use” individuals who continue to use both ENDS and combustible tobacco products.

Public Health England highlighted research showing that e-cigarette use can encourage smokers to reduce their consumption even if quitting smoking was not their initial motivation for starting to use ENDS. Undoubtedly because much of the harm of cigarette smoking results from even very minimal combustible tobacco use (as little as 3 cigarettes a day), the dual use of e-cigarettes and conventional cigarettes is clearly less beneficial for smokers’ health than quitting combustible cigarettes completely, if it is beneficial at all (ie, the health rewards of reduction are limited, and few experts promote it except as a step toward cessation; see Hurt et al,\textsuperscript{106} Simmons et al,\textsuperscript{107} and Pisinger and Gottfredsen\textsuperscript{108} for the effects or noneffects of reduction).

Summary and Discussion: ENDS and Smoking Cessation

There is some limited evidence that e-cigarettes and similar products may offer utility in helping some smokers to quit. In general, the existing research—although limited—suggests...
that, without behavioral counseling, they are probably approximately as effective as NRTs like the patch. More research, which is already underway, will continue to address this question. For example, the FDA and the National Institutes of Health have cosponsored a large research funding effort in their Tobacco Centers of Regulatory Science program, which is beginning to generate research relevant to these questions.

Dual Use

The impact of e-cigarette use on smoking behavior depends on causal links to gateway initiation, cessation, and ex-smokers returning to smoking. However, most gateway pathways, and many cessation pathways, theoretically involve some length of time when individuals use both e-cigarettes and tobacco cigarettes. The most recent US estimates suggest that a majority of adults who use e-cigarettes also smoke. How should we understand dual use as it relates to previously considered phenomena, such as gateway and cessation, as well as a dangerous, discrete category of behavior?

The direct harm from dual use, in most cases, is indistinguishable from the harms of smoking in general. A medium-term biomarker study has shown that, while complete switching to either NRT or e-cigarettes overwhelmingly reduces exposure to tobacco-related toxicants, dual use is not associated with any reduction compared with individuals who only smoke. Shorter term studies have shown reductions in toxicants for dual users that are commensurate with the reduction in cigarettes smoked. However, even if dual users displace some tobacco cigarette smoking without adding to nicotine consumption, which represents something of a best-case scenario, then this may still be of limited potential benefit. The main way that a smoking reduction would be convincingly clinically beneficial is if it represented a stepping stone to complete cessation.

Because there is no appreciable benefit to dual use otherwise, many public health professionals are concerned that dual use may make the problem worse. First, many youths are dual users, and approximately 1 in 6 youths who started out only vaping were dual users a year later, so it may be that dual use occurs among youth as part of a causal gateway pathway. Second, if adult dual users are smokers who would otherwise have quit, then perhaps, by undercutting the effectiveness of smoking bans, dual use could lead to reduced cessation. It is possible that applying smoke-free policies to ENDS could reduce the likelihood of this outcome, but there has been no published research testing this hypothesis.

As in the discussion of gateway effects, our inability to know or even convincingly estimate the counterfactual for dual users makes it difficult to draw any firm conclusions about whether dual use might hinder cessation efforts. Once again, there is a strong potential for confounding, such that comparisons of dual users with smokers who do not use e-cigarettes will not yield meaningful causal estimates. In this case, there are 2 related selection mechanisms. Dual users may be less likely to have initiated use of e-cigarettes with the intention of quitting smoking than e-cigarette users or former e-cigarette users who no longer smoke. Also, those who did use e-cigarettes to quit smoking, whether that was their initial intention or not, are no longer defined as dual users. Thus, likely quitters will select out of the dual-using population in at least 2 related ways.

It will be important to monitor dual users going forward, both because they comprise most ENDS users in the United States and some other countries and because many causal pathways into and out of smoking could plausibly involve a period of dual use. Given the evident disparity in health effects between complete switching and dual use, it is imperative that messaging from health authorities emphasize the harm from any amount of combustible cigarette smoking. Some dual users may believe that their smoking reductions are more clinically meaningful than the evidence suggests, so it is necessary to send a clear message that continued combustible smoking in any form is intolerably dangerous. Some will be concerned that such messaging may suggest that e-cigarette use alone is not harmful, but it should be possible to accurately convey the harms of e-cigarettes without obscuring the finding that dual use is far more harmful.

Summary and Discussion: Dual Use

The research suggests strongly that medium-term and long-term dual use or poly-use does little to reduce the harm from smoking only combustible tobacco products. However, dual use appears to be a poorly understood, complex phenomenon: for some, it appears to be a transition toward cessation; whereas, for others, it appears to be an opportunity to use nicotine in situations where combustible use is not permitted or acceptable. For other individuals, there appears to be a misunderstanding about how similar dual use is to continuing the use of only combustible products. More research is needed on dual use but, in the interim, there needs to be clear messaging about the harm of medium-term or long-term dual use.

Smokeless Tobacco

This report concentrates mainly on the newer category of ENDS products, but we include this discussion of smokeless tobacco to provide some additional perspective, both to this long-established noncombustible product class and to its relevance to the discussions around harm reduction. In particular, there have been claims of success—particularly in
Sweden—using smokeless tobacco products as a harm-reduction tool.

Smokeless tobacco is used around the world in a wide variety of forms, either on its own or as a substitute for combustible tobacco. Overall, less than 4% of US adults are current users (in the last 30 days) of smokeless tobacco. The highest prevalence (16%) is found among American Indian and Alaska Native males.115

The main forms of smokeless tobacco products used in the United States are snuff (moist and dry) and chewing tobacco (available in loose-leaf, plug, and twist formulations). The products sold by the major US tobacco companies have been evolving, including Swedish-style snus—a moist snuff that does not require spitting—and dissolvable products in the form of lozenges and pellets. A smokeless product known as Iq’milik, which is prepared from fire-cured tobacco leaves mixed with tree fungus ash, is used widely by Alaska Natives. Snus products available in the United States are sold by the major US tobacco companies under the brand names Marlboro, Camel, and Lucky Strike, among others (see Piano et al116).

Nicotine is present in all smokeless tobacco products, although the nicotine content varies across the many different types of products. The CDC analyzed 18 smokeless tobacco products available in the United States and found that, on average, moist snuff contained the highest nicotine content, while chewing tobacco contained the lowest.117

The carcinogenic compounds present in smokeless tobacco vary considerably, depending on the type of product and the manufacturing process. Overall, 28 carcinogens have been rigorously identified across a range of major smokeless tobacco products, primarily from 3 groups of compounds: nonvolatile, alkaloid-derived TSNAs; N-nitrosamino acids; and volatile N-nitrosamines.118 Among these carcinogens, researchers identify TSNAs as the most abundant in smokeless tobacco and the most carcinogenic.119 Other carcinogenic compounds include volatile aldehydes, polycyclic aromatic hydrocarbons, certain lactones, urethane, and various metals. There are smokeless products common outside the United States that are more harmful—smokeless tobacco users in Asia often chew it with areca nut or betel quid, which elevates the hazard profile of that form of chewing tobacco, because areca nut and betel quid are carcinogenic to humans.120

Smokeless tobacco use can cause precancerous oral lesions and is associated with oral, esophageal, and pancreatic cancer.118 Other health problems include oral leukoplakia, loosening of teeth, and irreversible gingival recession.118 Pregnant women are cautioned against using smokeless tobacco because of the potential negative effects on the unborn fetus.121

Swedish snus (a form of moist snuff) delivers levels of nicotine comparable to those of cigarettes but contains lower levels of TSNAs. A review in 2008 indicated that the total level of TSNAs for the US brands Taboka, Marlboro Snus, and Camel Snus was lower than the total TSNAs found in Swedish General Snus, whereas Skoal Dry products (regular and cinnamon flavor) contained much higher TSNAs levels than Swedish General Snus.119

Snus in Sweden (which may have compositional differences from the snus sold in the United States) has been credited by many with reducing smoking prevalence. Foulds et al121 point to the relative trends in male and female tobacco product use. Male smoking declined more substantially than female smoking in Sweden, and far more men than women were using snus during this time period. Tomar et al122 dispute that snus was responsible for the relative decline in male smoking, suggesting instead that workplace smoking regulations might have had a differential impact because more men were working outside the home (and thus were subject to such regulations), although such a differential has not been observed in countries with workplace sex composition and smoke-free regulations similar to Sweden’s. Sweden’s National Survey of Public Health reported in 2012 that the rate of daily snus use was 19% for men and 4% for women, whereas the Swedish government reported in their last MPOWER report that the daily smoking rate was 10.6% for men and 13% for women. Sweden has among the lowest adult smoking prevalence rates in high-income countries.28,123

In November 2015, the FDA authorized the sale of Swedish snus in the United States. To be marketed and labeled as an MRTP in this country, the firm Swedish Match (Stockholm, Sweden) applied for authorization through the FDA.123 In December 2016, the FDA acted on the Swedish Match application, denying one request and deferring final action on 2 additional requests, with the recommendation to amend the applications. The FDA denied the request to remove a required warning label stating that the products can cause gum disease and tooth loss based on the scientific evidence that these products, in fact, can cause gum disease and tooth loss. The FDA deferred action on the requests to remove a required warning label stating that their products can cause mouth cancer and to revise a required warning to state that their products pose substantially lower risks to health than cigarettes, instead recommending that Swedish Match could amend its application to modified-risk claims based on the scientific evidence. In addition, based on its first experience with an MRTP applications, the FDA provided additional guidance to manufacturers intending to submit such applications.

Stepanov et al125 analyzed TSNAs levels in American-brand smokeless tobacco products (Ariva, Stonewall, Exalt,
Revel, Smokey Mountain, and Quest) compared with nicotine-replacement products. The authors observed that nicotine-replacement products contained only trace amounts of TSNA. One tobacco-free snuff product, Smokey Mountain, did not contain any TSNA. Levels of TSNAs varied among the remaining products.\textsuperscript{125}

Various reviews have concluded that the magnitude of the hazards associated with smokeless tobacco is much lower than that associated with cigarette smoking. A 2007 review by the RCP indicated that smokeless tobacco has little or no effect on the risk of chronic obstructive pulmonary disorder and lung cancer and that, compared with cigarette smoking, “...the hazard profile of lower risk smokeless products is very favorable”\textsuperscript{28} (see also Benowitz\textsuperscript{126}). A 2008 review by the European Scientific Committee on Emerging and Newly Identified Health Risks concluded that smokeless tobacco users are at one-half the risk of cigarette smokers of developing cardiovascular disease.\textsuperscript{127} A review by the American Heart Association in 2010 also concluded that, “the evidence is consistent with the suggestion that the cardiovascular risks are lower with smokeless tobacco products.”\textsuperscript{116} Similarly, Roth et al systematically reviewed the literature and found that the cardiovascular risk associated with Swedish snus was markedly lower than the risk associated with cigarette smoking (although “markedly” is not well defined in the study). The same review also indicated that, based on the findings from a small number of studies, the health risks associated with snus are lower than those associated with smoking for lung cancer, oral cancer, gastric cancer, and all-cause mortality.\textsuperscript{128}

A 9-member panel of health experts estimated the relative risk of mortality associated with the long-term use of low-nitrosamine smokeless tobacco (LN-SLT) compared with long-term cigarette smoking. The panel estimated that at least a 90% reduction in total mortality risk was associated with LN-SLT use relative to cigarette smoking. For specific diseases, the median relative risk was highest for oral cancer (estimated, 0.15–0.30) and lowest for lung cancer (estimated, 0.02–0.03). For heart disease, the relative risk was estimated at 0.10. Because of the paucity of available data, the panel was unable to estimate the mortality risk associated with switching from cigarette smoking to LN-SLT or the risk associated with dual use of cigarettes and smokeless tobacco.\textsuperscript{129}

Given the profile of refined smokeless tobacco in relation to cigarettes and other combustible tobacco, the former has been suggested to potentially provide a safer alternative source of nicotine for smokers.\textsuperscript{116} However, the 9-member panel cited above\textsuperscript{129} cautioned against interpreting their findings as consensus that LN-SLT is an acceptable alternative to cigarette smoking. The panel asserted that to arrive at such a conclusion would require further evaluation of how such products are being used, by whom, under what circumstances, and whether the use of smokeless tobacco serves as a gateway to conventional smoking. Furthermore, there is a wide variety of smokeless products in the United States with various characteristics. Although smokeless tobacco is less hazardous than combustible tobacco, it is more harmful than NRT. For this reason, it has been suggested that clinicians should avoid recommending smokeless tobacco products to their patients who wish to quit smoking, because NRT is an effective and safer alternative.\textsuperscript{116,130}

\section*{Summary and Discussion: Smokeless Tobacco}

The vast preponderance of research suggests that the use of smokeless tobacco products causes less harm—and considerably less harm for some products—to an individual compared with the use of combustible tobacco products. Although there is significant risk for cancers of the oral cavity, nasal cavity, pharynx, and esophagus; for some other cancers; and for heart disease, smokeless tobacco is much less of a risk factor compared with combustible tobacco products. Despite the arguable success in Sweden, most experts in the United States have hesitated to recommend any such product (even Swedish snus) as a harm-reduction product, because it is more harmful than using NRTs. Furthermore, the regulatory and cultural environments between Sweden and the United States are different, in addition to the historical associations, and the Swedish experience might be difficult to replicate in the United States. Experts continue to call for further evaluation of who is using these products, how they use them, under which circumstances, and whether the use of smokeless tobacco serves as a gateway to conventional smoking.

\section*{Conclusions}

Approximately 10 years into the ENDS era, debates about these products continue. As ENDS use has increased, countries around the world have taken a wide range of policy approaches, from outright bans to full market access with relatively permissive regulations.\textsuperscript{131} The array of policy approaches reflects a continued range of opinion within the tobacco-control community. Not surprisingly, the lack of consensus also leaves many health professionals confused about how to counsel patients and, more generally, how to communicate accurately and meaningfully about ENDS.

Researchers have already generated a lot of excellent information about ENDS that can help us understand better the considerable complexity of the issues. Accordingly, in this review, we have sought to introduce not only the main debates and issues but also the scientific discussions occurring around them. Giving due consideration to the totality of available evidence, there remains a considerable range of reasonable disagreement about the overall
population health effects of ENDS and, thus, how they can best be regulated. There is also continuing debate about health effects on individuals. Although we have not generally attempted to resolve debates in which the evidence does not paint a clear picture and have eschewed specific policy proposals or clinical recommendations, our main recommendation is to be vigorous in the avoidance of false, misleading, or deceptive messaging. Put in a more positive way, messaging that seeks to be truthful, comprehensive, and thoughtful—which can mean the presentation of competing interpretations of the same data and/or analyses—helps to inform the public and build trust in the organizations, institutions, and individuals that disseminate health information. Thus, the goal of this review is to lay out the key debates around ENDS and the science that undergirds them in an accessible manner that first acknowledges the complexities, then seeks to disentangle them meaningfully for the reader.

Often, views on ENDS vary based on the subpopulation under focus. For subpopulations that are particularly harmed by nicotine itself, such as youth and pregnant women, ENDS might appear more threatening because, under certain circumstances, they could increase the probability of exposure to nicotine itself—particularly for never-nicotine users who begin using nicotine products only because of ENDS. For subpopulations in which smoking rates remain stubbornly high—those with mental illness, members of the military, people with low levels of educational attainment, and people in lower socioeconomic groups, among others—some argue that ENDS might potentially provide a much-needed alternative to tobacco cigarettes that may be far more realistic and/or appealing than conventional forms of NRT because of product characteristics, cost, or ease of access. Although smoking prevalence has declined over the last 20 years or more, cessation rates remain stubbornly low. While research to identify more effective cessation strategies continues, the evidence suggests that it is not happening quickly or easily.

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