

Electronic Nicotine Delivery Systems: A Policy Statement from the American Association for Cancer Research and the American Society of Clinical Oncology

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Abstract

Combustible tobacco use remains the number one preventable cause of disease, disability, and death in the United States. Electronic nicotine delivery systems (ENDS), which include e-cigarettes, are devices capable of delivering nicotine in an aerosolized form. ENDS use by both adults and youth has increased rapidly, and some have advocated these products could serve as harm-reduction devices and smoking cessation aids. ENDS may be beneficial if they reduce smoking rates or prevent or reduce the known adverse health effects of smoking. However, ENDS may also be harmful, particularly to youth, if they increase the likelihood that nonsmokers or former smokers will use combustible tobacco products or if they discourage smokers from quitting. The American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) recognize the potential ENDS have

to alter patterns of tobacco use and affect the public's health; however, definitive data are lacking. AACR and ASCO recommend additional research on these devices, including assessing the health impacts of ENDS, understanding patterns of ENDS use, and determining what role ENDS have in cessation. Key policy recommendations include supporting federal, state, and local regulation of ENDS; requiring manufacturers to register with the FDA and report all product ingredients, requiring childproof caps on ENDS liquids, and including warning labels on products and their advertisements; prohibiting youth-oriented marketing and sales; prohibiting child-friendly ENDS flavors; and prohibiting ENDS use in places where cigarette smoking is prohibited. *Clin Cancer Res*; 21(3); 1–12. ©2015 AACR. American Association for Cancer Research and American Society of Clinical Oncology.

Introduction

Tobacco is the number one preventable cause of disease, disability, and death in the United States. Combusted tobacco, which contains more than 7,000 chemicals, including hundreds of toxic compounds (1), is particularly dangerous. The 2014

Surgeon General's Report (SGR) reaffirmed the overwhelming adverse health effects of smoking, which has resulted in 20,000,000 premature deaths since 1964 (2). An estimated 484,000 people in the United States die prematurely from smoking-related illnesses each year; 5.6 million children alive today

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Prevention Committee (CaPC). The statement was reviewed by both parent committees (i.e., the AACR SPGA Committee and the ASCO CaPC), and was approved by the AACR Boards of Directors on August 6, 2014, and the ASCO Executive Committee on September 18, 2014. This policy statement was published jointly by invitation and consent in both *Clinical Cancer Research* and *Journal of Clinical Oncology*. Copyright 2015 American Association for Cancer Research and American Society of Clinical Oncology. All rights reserved. No part of this document may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, recording, or storage in any information storage and retrieval system, without written permission by the American Association for Cancer Research and the American Society of Clinical Oncology.

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will die prematurely if current smoking trends continue (2). Smoking causes 18 forms of cancer and accounts for 30% of all cancer deaths in the United States. It is also a known cause of numerous other diseases and conditions. The risks of lung cancer have increased in both men and women over the past 50 years as a result of changes in the design and composition of cigarettes (2). Moreover, continued smoking by cancer patients and survivors reduces the effectiveness of cancer treatments and causes increased overall mortality, cancer-specific mortality, and risk for second primary cancer (2, 3). Preventing tobacco use initiation and facilitating cessation are the best ways to combat the problems caused by smoking. Smokers who quit greatly reduce their risk for disease and premature death, and smoking cessation improves cancer patients' outcomes (2). Clear evidence demonstrates that mass media campaigns, comprehensive community-based programs, and statewide tobacco control programs reduce the prevalence of tobacco use among all age groups (2), which has resulted in tobacco use becoming a less socially acceptable behavior over the past 50 years. Reductions in tobacco use are followed by subsequent reductions in chronic disease (2); however, given the delayed time course needed to assess the adverse impacts of cigarette smoking and health benefits associated with cessation, evaluating the health effects of electronic nicotine delivery systems (ENDS) should be conducted in a more timely manner than was done with cigarettes.

There is agreement that eliminating the use of combustible tobacco products would improve public health substantially. However, there is less agreement as to whether ENDS should be used as a substitute for smoking among those who experience difficulty quitting or do not want to quit. ENDS, including electronic cigarettes (e-cigarettes), are battery-operated devices capable of delivering nicotine in an aerosolized form. ENDS do not combust tobacco or contain the same number or concentrations of carcinogens and toxicants found in cigarette smoke. They may, therefore, have value as harm-reduction devices and tobacco-cessation interventions (4). Indeed, many smokers report using ENDS to reduce and/or stop smoking (5). ENDS may be beneficial if they reduce smoking rates or prevent or reduce the known adverse health effects of smoking. However, ENDS may be harmful, particularly to youth, if they increase the likelihood that nonsmokers or former smokers will use combustible tobacco products or if they discourage smokers from quitting. Although ENDS are being marketed with health claims and smoking-cessation messages (6), there are insufficient data at this time on the long-term health consequences of ENDS to all segments of the population, their value as tobacco cessation aids for current smokers, and their effects on the use of combustible tobacco products by nonsmokers and current smokers. Moreover, our understanding of ENDS is changing rapidly as use increases and products evolve, making it difficult to interpret the evidence, because conclusions based on studies conducted a few years ago may not apply to the marketplace today.

The American Society of Clinical Oncology (ASCO) and the American Association for Cancer Research (AACR) are leading professional societies for clinicians and researchers in the field of oncology, both with a focus that includes preventing and curing cancer through research, education, communication, and collaboration. As a new nicotine delivery technology with the unknown but potentially significant ability to alter patterns of tobacco use and its attendant public health consequences, ENDS are of particular interest to ASCO and AACR. Our organizations convened

an expert panel to develop a joint policy statement with the following goals:

1. educating policymakers, oncologists and other health care providers, researchers, and the public on the major public health and policy issues relevant to ENDS;
2. outlining the clinical concerns oncologists and other health care providers face when encountering a patient who uses or expresses interest in ENDS;
3. identifying key research necessary to build a more complete evidence base for understanding the safety profile and public health impact of ENDS and for informing ENDS regulation and possible patient care; and
4. providing recommendations to policymakers for regulating ENDS.

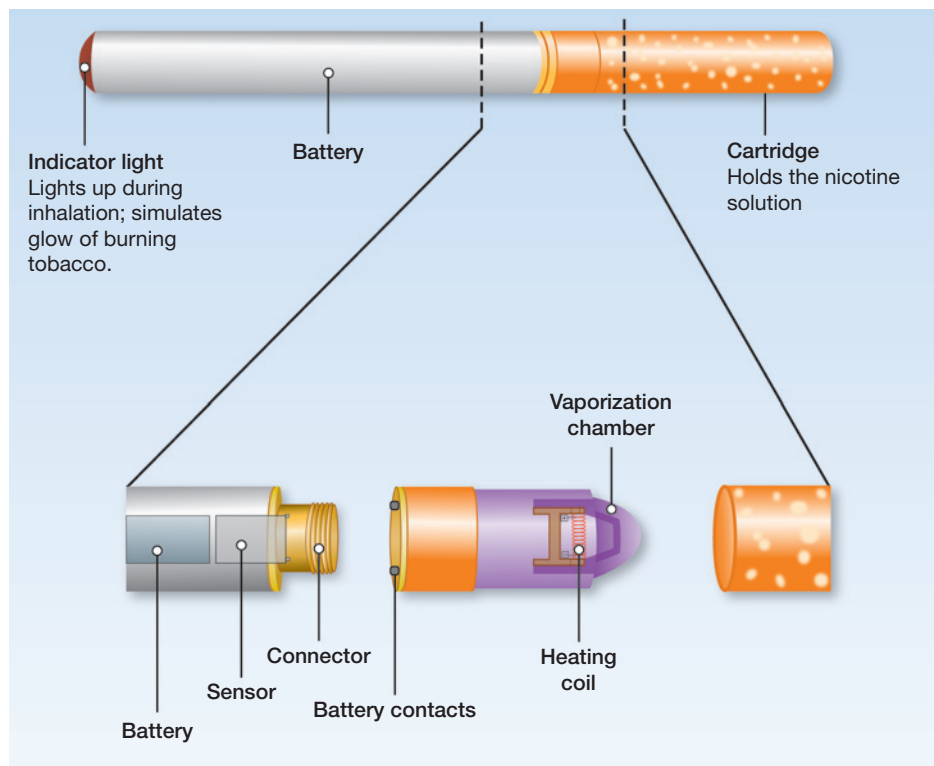
What Are Electronic Nicotine Delivery Systems?

ENDS are designed to deliver nicotine with fewer toxicants and carcinogens than traditional cigarettes by vaporizing a nicotine solution instead of combusting tobacco. In automatic ENDS models (Fig. 1), when a user inhales from the device, air flow is detected by a sensor, which activates a heating element that aerosolizes a solution (i.e., creates a fine mist of liquid droplets, often referred to as a vapor) typically containing nicotine that is stored in the mouthpiece cartridge. In manually operated models, a heating element is activated by pressing a button. Some models include a light-emitting diode (LED) that is activated during inhalation and simulates the glow of burning tobacco.

The first ENDS products appeared in the U.S. market in the first decade of 2000 and were initially imported from China and distributed online by independent companies. These products have evolved rapidly in recent years, as the market has changed and products have become more available and more sophisticated (7). At the time of this publication, there are more than 460 ENDS brands, with more than 7,700 flavors available on the Internet. Rechargeable and disposable e-cigarettes are often referred to as first-generation ENDS, while tank systems and personal vaporizers are referred to as second- and third-generation products, respectively. First- and second-generation devices are typically distributed via convenience stores, pharmacies, and gas stations. There are a number of independent companies that sell only ENDS products (mostly second-generation tank systems), but major tobacco companies have begun to market their own ENDS brands as well, usually consisting of first-generation disposable or rechargeable products. Third-generation devices (personal vaporizers) are typically sold at local shops, commonly called "vape shops" or "vape lounges." A fourth-generation "digital" delivery device became available nationally earlier this year (8). ENDS differ primarily in appearance, the nature and concentration of the nicotine solution, the capacity of the cartridge or reservoir (so-called "tank") containing the solution, the nature of the heating element, and the size and type of battery (Fig. 2). Propylene glycol and glycerin are the primary solvents for the nicotine. The solution may contain either or both solvents mixed with water. Various additives and flavorings are commonly added to the solution, including fruit and candy flavors, various sugars, ethyl alcohol, and nonnicotine pharmacologically active compounds and stabilizers. The heating elements are usually thin wire made with various metals (nickel, chromium, copper coated with

Figure 1.

Basic components and operation of electronic nicotine delivery systems (ENDS). When a user inhales from the ENDS device, air flow is detected by a sensor. The sensor activates a heating element that pulls the e-liquid stored in the cartridge into the vaporization chamber, where it is aerosolized (i.e., turned from e-liquid into a fine mist of liquid droplets, often referred to as a vapor). The aerosolized e-liquid is then inhaled by the user. In some models, activation of the sensor also powers the indicator light, which simulates the glow of burning tobacco. In manually operated models, the heating element is activated by pressing a button.



silver). These engineering features affect the chemical composition and potential toxicity of the ENDS aerosol (9, 10).

Research reports on ENDS focus primarily on e-cigarettes and are largely limited to reports on self-selected groups of ENDS users. Long-term users report that they had started with cigarette-like ENDS products and progressed to more sophisticated devices. One study reported that novice users usually buy e-cigarette "starter kits" containing a basic model of the device, a battery charger, liquid refills, and instructions. Experienced users often seek a variety of batteries, atomizers, and liquids, which may not resemble traditional cigarettes, and may include longer-lasting and higher-voltage batteries capable of vaporizing a larger amount of liquid and producing a "throat hit" preferred by some users (11). The numerous colors, artistic designs, carrying cases, and accessories for ENDS support a variety of individual styles.

Although definitive data are lacking, nicotine from ENDS is likely absorbed through the upper aerodigestive tract through mucosal surfaces or lung parenchyma that are in direct contact with ENDS aerosol. At this time, it remains unclear how effectively various ENDS deliver nicotine. Furthermore, some ENDS contain no nicotine or virtually no nicotine. At least four factors affect the amount of nicotine from ENDS absorbed into the blood stream and reaching the nicotinic receptors in the brain: (i) the nicotine content in a product; (ii) how effectively the vaporization process transfers nicotine from the reservoir into the aerosol; (iii) additives that may facilitate nicotine absorption; and (iv) use habits (such as frequency and depth of inhalation) that may affect the bioavailability of nicotine. Some studies suggest large between-brand and within-brand differences in nicotine vaporization (12–14). The differences are likely to be a function of different types of heaters reacting differently to the spacing and frequency of puffs

employed in the studies. Other factors affecting nicotine bioavailability are product characteristics such as cartridge size, battery strength, aerosol pH, and draw resistance. For example, some ENDS have cartridges that contain levels of nicotine similar to other brands, but the aerosol contains substantially lower levels (14). Early models tended to deliver relatively low doses of nicotine compared with cigarettes, but newer devices using high-nicotine-concentration solutions might deliver nicotine at levels comparable with those derived from cigarettes (15–19). In addition to delivering nicotine, the aerosol may also provide a flavor and physical sensation sought by many smokers that are similar to those of inhaled combustible tobacco smoke.

Current Regulation of ENDS

The policy environment for ENDS is rapidly changing, and regulation of these products varies widely around the world. At the time of this publication, ENDS containing nicotine derived from tobacco fall within the statutory definition of tobacco products within the United States as long as manufacturers do not make therapeutic claims that would qualify them as "drugs" or "drug delivery devices." Unlike combustible cigarettes, however, ENDS are not yet regulated under the FDA tobacco regulatory authority. As a result, there is a lack of mandatory manufacturing standards for ENDS, and few quality controls are in place (20). The FDA recently released a proposal (21) to extend its regulatory authority over ENDS. If it is adopted, the rule would give the agency authority to regulate the manufacturing, distribution, and marketing of these products, including requiring ENDS manufacturers to report product and ingredient listings; require public health warnings on products and advertisements; prohibit manufacturers from marketing new ENDS products prior to FDA






ENDS type	Product characteristics
Disposable e-cigarette 	<ul style="list-style-type: none"> • For short time use • Cheap; widely available from gas stations or super markets • Convenient as no refill solution or cartridge is needed • Might be a starting point for many users
Rechargeable e-cigarette 	<ul style="list-style-type: none"> • Various sizes from cigarette size, to compact flashlight size • Various colors and styles • Requires battery with a charger • Requires replacing or refilling nicotine cartridges
Tank system e-cigarette 	<ul style="list-style-type: none"> • High-capacity • Battery operated • Lasts longer than typical rechargeable models • Requires refilling the tank with nicotine solution • Often recommended for heavy smokers by retailers
Personal Vaporizer 	<ul style="list-style-type: none"> • Large size and heavy weight • Battery power output control allows the user to adjust the output of the voltage going to the heating element, which has a direct effect on the temperature of the heating element • Usually not recommended by retailers for beginning users
E-cigar 	<ul style="list-style-type: none"> • Looks like an authentic large cigar • Usually disposable

Figure 2.

Overview of various types of electronic nicotine delivery systems (ENDS). This figure lists and describes examples of ENDS on the market. ENDS and ENDS refill solutions are available in a wide variety of flavors, and the products are rapidly evolving.

review; and prohibit manufacturers from making direct and implied claims of reduced risk in the absence of scientific evidence supporting a public health benefit (Table 1). The FDA has also proposed to prohibit distribution of free samples of ENDS products, sales to youth, and sales through vending machines, except in adults-only facilities. Although the Agency may choose to do so in the future, the FDA's proposal does not impose restrictions on the advertising, marketing, or promotion of ENDS or impose ENDS products standards such as a ban on characterizing flavors (both of which apply to combustible cigarettes, though menthol-flavored cigarettes are permitted). In the absence of federal regulations, both advertising (6, 22) and flavored ENDS (7) have proliferated. At the time of publication, over 7,700 e-cigarette flavors were available (7) and youth and young adult exposure to e-cigarette advertising on television increased by 257% and 321%, respectively, from 2011 to 2013 (23). The FDA does not have the authority to tax ENDS or restrict their use in public spaces, though

states and local jurisdictions may do so. Indeed, many have already taken action to regulate ENDS, including imposing restrictions on the sale of ENDS to minors and prohibiting use of ENDS in public places (24, 25). Currently, only one state, Minnesota, explicitly includes e-cigarettes in their tobacco tax regulation; this regulation equates to 95% of the product's wholesale cost (25). Comparatively, every state taxes cigarettes, with tax rates ranging from \$0.30/pack in Virginia to \$4.35/pack in New York (26). Federal excise taxes for cigarettes are currently at \$1.01/pack (26).

What Are the Public Health Effects of ENDS?

Toxicity

Of the relatively few research reports on the safety of ENDS, most involve e-cigarettes. Although e-cigarettes do not contain

Table 1. Major provisions of FDA's proposal to extend its regulatory authority over E-cigarettes

In April 2014, the FDA released a proposal to extend its regulatory authority over e-cigarettes using the agency's authority under the Family Smoking Prevention and Tobacco Control Act. If adopted the proposed rule would give the FDA authority to regulate the manufacturing, distribution, and marketing of these products.

The proposed rule would

1. prohibit the sale of e-cigarettes to individuals aged under 18 years and require retailers to verify the birth date of any purchaser under the age of 26 years by reviewing the individual's photographic identification;
2. prohibit the distribution of free samples of e-cigarettes;
3. prohibit the sale of e-cigarettes through vending machines except in adults-only facilities; and
4. Require e-cigarette manufacturers to do the following:
 - a. register with the FDA and report all product and ingredient listings, including harmful and potential harmful components;
 - b. only market new tobacco products after FDA review;
 - c. only make direct and implied claims of reduced risk if the FDA confirms that scientific evidence supports the claim and that reduced risk product marketing will benefit public health as a whole; and
 - d. include the following health warning on e-cigarette packaging and advertising: "WARNING: This product contains nicotine. Nicotine is an addictive chemical."

Note: The proposed rule would not prohibit the sale of flavored e-cigarettes; restrict advertising, marketing, or promotion of e-cigarettes; impose taxes on e-cigarettes; or impose restrictions on indoor e-cigarette use.

many of the toxic substances in cigarette smoke, a recent FDA review (12) reported that various chemical substances and ultra-fine particles known to be toxic, carcinogenic, and/or to cause respiratory and heart distress have been identified in e-cigarette aerosols, cartridges, refill liquids, and environmental emissions. Another study found that the levels of the toxicants in e-cigarettes were significantly lower than in cigarette smoke and, in many cases, comparable with trace amounts found in a medicinal nicotine inhaler (27). It is important to note that there is wide variation in product components and methodologies used in these studies, and methods for assessing toxicants in ENDS are not well validated (12). Moreover, the effects these toxicants might have on ENDS users after chronic and frequent use of the devices remain unclear, and there are several unanswered health questions, such as the pulmonary effects of propylene glycol, glycerin, and other constituents of ENDS.

Nicotine is the compound in tobacco that can cause addiction (28), and like combustible cigarettes, many e-cigarettes deliver nicotine. The 2014 SGR concludes that nicotine activates multiple biologic pathways through which smoking increases risk for disease, that nicotine adversely affects maternal and fetal health during pregnancy, and that exposure to nicotine during fetal development has lasting adverse consequences for brain development (2). Moreover, evidence suggests that nicotine exposure during adolescence may have lasting adverse consequences on the developing brain.

Nicotine is a known potentially lethal toxin, and poisoning related to ENDS can occur by ingestion, inhalation, or absorption through the skin or eyes. Concerns have been raised that ENDS can harm their users by delivering toxic nicotine levels. Nicotine levels can be assessed by measuring cotinine, a nicotine metabolite and validated biomarker of nicotine uptake (17). Two pilot studies measured saliva cotinine levels in samples collected from ENDS users and found high levels of cotinine, suggesting that experienced ENDS users are able to gain as much nicotine from ENDS as

smokers do from cigarettes (17, 29). The observed levels were similar to levels previously observed in smokers and higher than levels previously found in nicotine replacement therapy (NRT) users (17, 29). Other studies have shown that some ENDS users experience side-effects such as mouth and throat irritation which may be caused by exposure to nicotine itself, nicotine solvents, or toxicants found in the aerosol (30, 31). However, given the relatively low doses of nicotine that ENDS deliver, and users' ability to titrate the desired dose by adjusting the frequency and topography of their puffs, serious overdose from ENDS aerosol inhalation is unlikely. In contrast, the concentrated nicotine in ENDS solutions can be toxic if it is inadvertently ingested or absorbed through the skin. Data from the Centers for Disease Control and Prevention (CDC) showed a significant increase in e-cigarette-related calls to poison centers; the number of calls rose from one per month in September 2010 to 215 per month in February 2014, with more than half of the calls involving young children (32).

Exposure to secondhand smoke from combustible cigarettes is an established health risk (2). There are no current data to suggest that second-hand exposure to ENDS has any health effects; however, second-hand exposure to ENDS vapor is possible. Although no sidestream aerosol is generated from ENDS between puffs, some of the aerosol is exhaled by the user, and e-cigarettes may expose nonusers to nicotine from secondhand exposure (33, 34). It has also been reported that e-cigarettes emit ultrafine particles, trace amounts of carbonyls, volatile organic compounds, polyaromatic hydrocarbons, tobacco-specific nitrosamines, and glycols into the indoor air (35, 36). However, other studies have found levels of dangerous substances that fall below Occupational Safety and Health Administration (OSHA) exposure limits (37). The emissions of nicotine and toxicants from e-cigarettes were significantly lower than those of combustible cigarettes. It has been estimated that second-hand exposure to nicotine from e-cigarettes is on average ten times less than from tobacco smoke, but the level of exposure depends on the brand (34).

Third-hand exposure occurs when nicotine and other chemicals from second-hand aerosol deposit on surfaces, exposing people through touch, ingestion, and inhalation (38, 39). Nicotine is very difficult to remove from surfaces, and while emissions of nicotine and toxicants from e-cigarettes are small compared with emissions from combustible cigarettes, they might still be a significant source of third-hand exposure (34, 35). There are no published studies evaluating third-hand exposure to ENDS aerosol in indoor environments, although preliminary data suggest that nicotine from ENDS can stick to surfaces (40).

The effects of second-hand ENDS use should not only consider health effects of exposure to the aerosol, but also the effects it may have on an individual's desire to smoke. One study found that exposing young adult daily smokers to e-cigarette use by others in an experimental setting increased their desire to smoke combustible and e-cigarettes (41).

Abuse liability

Nicotine is the primary addictive component of tobacco. Knowledge about the addictiveness or abuse liability of ENDS is important as a means to determine the potential for continued and persistent use of these products, the extent to which they can substitute for cigarettes, and how difficult it will be for ENDS users to stop using these devices after they start. Although some ENDS do not contain nicotine, surveys show that 97% of respondents

who use e-cigarettes use products containing nicotine (42). However, research on the abuse liability of ENDS is complicated by variation among product composition and use patterns. In addition to variable nicotine delivery within and across brands (43, 44), nicotine delivery varies by the users' level of experience with these products, with more experienced users obtaining levels of nicotine comparable with those achieved by cigarette smokers (17, 19, 45). However, the rate of absorption, an important factor contributing to the abuse liability of a drug, may be slower for e-cigarettes compared with conventional cigarettes (15), which may lessen the abuse potential of e-cigarettes compared with combustible cigarettes. The sensory aspects of ENDS use may also affect abuse liability. For example, Eissenberg (45) observed that despite the minimal increase in plasma nicotine from the e-cigarettes, there was a significant decrease in craving with the use of these products. Another study showed a reduction in self-reported stages of addiction whether or not the e-cigarettes contained nicotine (46). To date, no study has carefully investigated the effect of different nicotine doses of e-cigarettes to determine participant preference and effect. Furthermore, new generations of e-cigarettes are likely to improve nicotine delivery, and studies with these newer products are warranted.

Who Is Using ENDS and Why?

When considering patterns of ENDS use, it is helpful to address adults and youth separately. Within either population, *de novo* use of ENDS by nonsmokers would present a public health concern, but this is a particular concern with respect to youth, especially if ENDS serve as a pathway to other tobacco products, including combustible cigarettes, or renormalize cigarette smoking. With adults, the primary issue is the degree to which ENDS use by current smokers represents harm reduction (via smoking cessation or smoking reduction) versus harm escalation (by promoting greater nicotine intake through dual use and/or continued tobacco use). Current research to date cannot offer strong evidence with respect to these important public health issues, but it can provide a context to identify future population-based changes in use and guide the design of more informative longitudinal studies.

Youth ENDS use

A 2011 study conducted with a national sample of male adolescents reported low use of e-cigarettes (<1%). Approximately 18% of participants were willing to try e-cigarettes, and smokers were more willing to try them than were nonsmokers (47). National data on e-cigarette use by middle and high school students were gathered from the National Youth Tobacco Survey (NYTS) in 2011 and 2012 (48). Among middle and high school students, "ever use" of e-cigarettes (tried at least once) increased from 3.3% to 6.8%, whereas current use (within the past 30 days) increased from 1.1% to 2.1%. Among high school students specifically, current use rose from 1.5% to 2.8%. However, of the ever-users in high school, 80.5% reported current use of combustible cigarettes in 2012, suggesting that e-cigarettes are primarily attractive to current smokers. Another analysis of NYTS data from the same time period confirmed that current e-cigarette users were much more likely to be current smokers (49). Reasons for youth e-cigarette use are not well known at this time. Although absolute prevalence rates of e-cigarette use by youth are low, the proportional increase in current use is a concern.

Adult ENDS use

The overall use of ENDS by adults is low, with less than 2% reporting use every day or some days in 2012 and 2013, compared with 18% who report using cigarettes (50). Data on e-cigarette use by adults have been gathered primarily from Web-based surveys and convenience sampling, including regional samples, and from participants in online e-cigarette forums. Interpreting such data is difficult, but patterns suggest that e-cigarette prevalence is doubling annually and that the vast majority of e-cigarette users are smokers (51), with only about 1% lifetime prevalence among never smokers (52). At least 20% to 35% of current smokers have tried e-cigarettes (53–55), with the proportion increasing rapidly. A recent review concluded that no consistent differences in prevalence have been found with respect to sex, race/ethnicity, or age among adults, but low-income individuals appear more likely to have used e-cigarettes (52), a well-established pattern observed for cigarette use (2). Adults primarily report use of e-cigarettes to quit or reduce smoking, as e-cigarettes are perceived to be safer than combustible cigarettes (52). Moreover, users tend to report high satisfaction with the product (56).

Overall, patterns suggest that e-cigarettes are used primarily by smokers of combustible cigarettes, but ever-use by never smokers is higher among youth, raising concerns that this product may serve as an introduction to tobacco use among adolescents. Indeed, e-cigarette initiation by either youth or adult nonsmokers—including former smokers—is a cause for concern. Dual-use patterns appear to be common, and adults tend to report harm-reduction motivations for using e-cigarettes. However, existing data are rapidly evolving and are insufficient to clarify patterns of or motivations for ENDS use by youth or adults.

How does ENDS use affect smoking cessation?

In the United States, the FDA has not approved ENDS as smoking cessation aids. To date, only a handful of studies have explored the efficacy of using ENDS for smoking cessation. The major studies are listed in Table 2. In general, these data suggest that ENDS might be as effective as NRT in helping smokers quit, and several studies have found ENDS use to be associated with withdrawal relief after smoking cessation. However, these studies are inconclusive to support or refute the use of ENDS as a potential smoking cessation aid. Although a few larger studies are reported here, most studies were observational. The clinical trials tended to be small and lacked sufficient assessment of nicotine delivery, ENDS product evaluation, or formal instructions on how to optimize product use. Furthermore, the types of products evaluated by these studies are no longer reflective of current products on the market.

Dual use: Reducing cigarette use with ENDS

Dual use refers to the use of multiple tobacco products. Many ENDS users are dually using these products with combustible cigarettes, and several studies have found that ENDS use by cigarette smokers can reduce the number of cigarettes smoked (5, 42, 60–64). Although ENDS may deliver fewer toxic compounds compared with combustible cigarettes, the extent to which reducing exposure to these compounds would lead to meaningful reductions in adverse health effects is unknown. Prior studies show that reducing the number of cigarettes smoked by greater than 50% does not necessarily lead to health benefits (69, 70). While reducing smoking substantially may have health

Table 2. Major studies on the use of ENDS for smoking cessation

Authors (Reference)	Study type and population	Sample size	Results
Etter and Bullen (42)	Online survey of e-cigarette users recruited from websites who were current or former smokers of combustible cigarettes	3,567	<ul style="list-style-type: none"> - 92% of users who were current smokers reported e-cigarettes helped them to reduce smoking - 96% of former smokers reported the product helped them to quit smoking - 79% used e-cigarettes to deal with craving - 67% to deal with tobacco withdrawal symptoms
Brown et al. (57)	Survey of adults in the United Kingdom who tried to quit smoking in the past year	6,000	- cigarette users had a higher quit rate (20%) than those who used NRT (10%) or no smoking cessation aids (15%)
Adkison et al. (5)	Four-country cross-sectional survey of current and/or former smokers	5,939	85% of current e-cigarette users reported using them to quit smoking; only 11% reported having quit, and there were no significant differences in quit rates between e-cigarette users and nonusers
Vickerman et al. (58)	Survey of state telephone quit line participants registered for cessation services	2,758	E-cigarette users were less likely to quit smoking compared with never-users of e-cigarettes
Grana et al. (59)	National sample of current U.S. smokers recruited from a Web-enabled panel	1,549	E-cigarette use at baseline did not predict smoking cessation 1 year later among smokers regardless of whether they said they were using ENDS to quit or not
Polosa et al. (60, 61)	Observational study of smokers given access to e-cigarettes for 6 months	40	Found 23% and 13% abstinence rates at 6 and 24 months, respectively; rates did not substantially differ from those found in similarly designed observational studies using NRT products (78, 79)
Caponnetto et al. (64)	Clinical trial of smokers assigned e-cigarettes with and without nicotine	300	No significant differences in abstinence rates were observed between smokers assigned e-cigarettes with and without nicotine, and overall abstinence rates were similar to those found in trials in which NRTs were provided for 6 months or longer to reduce cigarette use (8-83)
Bullen et al. (46)	Clinical trial of adult smokers randomized to nicotine-containing e-cigarettes, nicotine patches, or non-nicotine-containing patches	657	No difference in abstinence rates were observed among groups at 6 months; quit rates in this trial were lower than expected for NRT, but the authors concluded that the trial was not sufficiently powered to draw conclusions on the effectiveness of e-cigarettes

benefits, it may also be difficult to achieve. One study demonstrated that in order to achieve a 42% reduction in exposure to carcinogens, about a 90% reduction in cigarettes smoked must occur (71). This result indicates that smokers trying to reduce the number of cigarettes they smoke tend to smoke each cigarette more intensely. The increased intensity occurred even when smokers were provided with NRTs. E-cigarette studies have shown that only 1% to 15% of those who continued to smoke reduced their usual brand smoking intake by around 90% (60, 64). The health benefits or harms of dual use are as yet undefined. On the other hand, if dual use with reductions in smoking is a path toward abstinence from cigarette smoking, then dual use can eventually lead to benefits in health.

Flavored ENDS

Flavored ENDS have proliferated, and more than 6,700 unique flavors are now on the market (7). Research shows that flavored tobacco is particularly appealing to youth, and some flavored combustible products potentiate continued use and addiction (72, 73). There is concern that flavored ENDS may have a similar effect on youth. Although it did not assess flavorants in general, a 2011 report from the Tobacco Products Scientific Advisory Committee (TPSAC) concluded that there was sufficient evidence that the availability of menthol cigarettes likely increases experimentation and regular smoking and increases the likelihood of addiction and degree of addiction in youth (72). However, some experts believe that the availability of flavored ENDS may encourage adult smokers to switch from combustible products to ENDS, prevent youth from transitioning from ENDS to combustible

products, and enhance the efficacy of ENDS as cessation aids. At present, the impact of flavored ENDS on patterns of use and smoking cessation is unknown.

What Are the Clinical Concerns for Oncology?

The AACR and ASCO strongly encourage health care providers to refer patients who use tobacco—including cancer patients—to evidence-based cessation treatment and recommend the use of FDA-approved cessation methods (3, 74, 75). Providers treating cancer patients should advise those who smoke that continued smoking can adversely affect their cancer treatment outcomes (2, 3).

Given the overall lack of evidence supporting the use of ENDS as a proven cessation aid for smokers in general, and the absence of any data on the potential adverse effects of inhaling ENDS aerosol by cancer patients undergoing treatment, oncologists would be wise to refrain from recommending ENDS as a first-line therapy for smoking cessation. However, given the wide-scale marketing of ENDS, providers should expect that patients may ask questions like the following: *Are e-cigarettes safe for use? Are e-cigarettes effective in helping to quit smoking? Can I use e-cigarettes along with NRT to help me quit or cut down?* In response to these queries, health care providers should commend their patients for their interest in quitting smoking and advise them that safe and effective cessation medications exist (76). Providers should explain that ENDS are not currently approved for smoking cessation by the FDA and that there is

wide variation in manufacturing and product design, as well as safety concerns for users and individuals exposed to ENDS aerosol. Currently, there is insufficient evidence to recommend ENDS to cancer patients, and the potential benefits or harms of ENDS use by cancer patients are unknown. A recent observational study of 1,074 cancer patients seeking cessation treatment in 2012 and 2013 found increasingly high rates of e-cigarette use (38.5% of combustible cigarette smokers reported e-cigarette use in 2013 vs. 10.6% in 2012) and no evidence that e-cigarette use was associated with superior cessation outcomes at follow-up (77). No controlled trials have examined the efficacy and safety of ENDS in cancer patients treated with surgery, chemotherapy, or radiotherapy. The potential interactions of ENDS with cytotoxic cancer therapeutics are also unknown, and there is *in vitro* evidence that nicotine stimulates proliferation, migration, invasion, and angiogenesis and decreases cancer cell death from irradiation and chemotherapy, raising concern as to whether prolonged ENDS use might have similar effects in patients with cancer (78). Moreover, researchers have found that human bronchial cells grown in medium exposed to e-cigarette aerosol showed a similar pattern of gene expression to those grown in medium exposed to tobacco smoke (79).

Whereas ENDS may have unknown adverse effects in cancer patients, the adverse effects of smoking are not in question. Recognizing the importance of providing guidance to physicians, the International Association for the Study of Lung Cancer has published recommendations for discussing e-cigarette use with cancer patients (80). Oncologists should advise all smokers to quit smoking combustible cigarettes, encourage use of FDA-approved cessation medications, refer patients for smoking cessation counseling, and provide education about the potential risks and lack of known benefits of long-term e-cigarette use.

Research Considerations for ENDS

The evidence regarding the risks and benefits of ENDS in different segments of the population, such as current smokers and nonsmokers, is difficult to interpret, as the marketplace of ENDS products is evolving rapidly and data on the long-term consequences of ENDS use are not yet available. Additional studies are needed to inform ENDS policy and regulation and to guide the decisions of consumers and health care providers related to ENDS use. Research in this field is complicated by the ever-changing and wide variability among and within products, a lack of standardized definitions of ENDS, variable user terminology, and a lack of established protocols for conducting ENDS research, including clinical trials. Despite the many challenges and gaps in our understanding, research on ENDS is progressing rapidly. A recent NIH workshop resulted in a comprehensive research agenda for studying these products (81). AACR and ASCO recommend research in the areas outlined below, some of which were discussed at the NIH workshop. Clinical studies should consider inclusion of healthy volunteers as well as vulnerable populations, such as children, pregnant women, cancer patients, and people with other acute or chronic medical conditions, and other underrepresented groups, where scientifically and ethically appropriate. Consistent with best practices, investigators should disclose potential conflicts of interest such as funding received from pharmaceutical, tobacco, and ENDS industry sources.

Analyzing ENDS products

1. **What are the key design features of ENDS products?** There are more than 460 ENDS brands, thousands of e-liquid alternatives on the market (7), and considerable variability in product design and performance (13). As a result, it is currently impossible to draw firm conclusions about the health risks of these products as a whole. Research is needed to understand how different design features relate to potential abuse liability and toxicity, for example, if the compounds in ENDS are affected by heating, changes in chemical composition, or pH; if these compounds are absorbed into the bloodstream; and how e-liquid additives affect the bioavailability of these compounds, among other considerations. Research is also needed to understand whether potential health risks may be ameliorated by changes in product engineering.
2. **How can ENDS product testing be standardized?** Considering the wide variation in ENDS products and performance, a standardized system for testing ENDS would help define likely performance boundaries for different products; allow for comparison among products in chemical compositions and biologic and health effects; and enable longitudinal tracking of changes in product design.

Assessing the health impacts of ENDS

1. **What are the health effects of acute and chronic ENDS product use, including second- and third-hand exposure?** *In vitro*, *in vivo*, and clinical studies are needed to develop biologic and clinical models of the physiologic effects of ENDS aerosol exposure. Studies should examine the efficacy and safety of ENDS in the general population and in cancer patients treated with surgery, chemotherapy, and radiotherapy, and how ENDS potentially interact with cytotoxic cancer therapies. The effect of ENDS use on treatment side effects, complications, response, and cancer recurrence also need to be examined. Relevant ENDS user outcomes should be examined relative to those individuals who continue to smoke, those who quit smoking, and those who use FDA-approved NRT products.
2. **Does transition from smoking to ENDS confer a health benefit?** The potential health benefits of using ENDS to eliminate or reduce the number of combustible cigarettes smoked should be examined in the general population and specific populations of interest, including cancer patients.
3. **What is the abuse potential of different types of ENDS?** Although nicotine is a highly addictive drug, research is needed to determine the addictive potential of ENDS as related to nicotine content and product design. Studies should examine how variability in the nicotine concentration of ENDS liquid, the amount of nicotine vaporized, and ENDS topography affect delivery of nicotine to users and how these compare with nicotine delivered by combustible cigarettes and FDA-approved NRT. Studies should also assess other factors that may contribute to potential abuse liability of ENDS, including nonnicotine additives and the sensory aspects of smoking.

Understanding the perception and patterns of ENDS use

1. **What are common patterns of ENDS use?** Research is needed to understand reasons for, and patterns of, ENDS

use among youth and adults, including how ENDS use affects use of combustible tobacco products. Research on ENDS use among cancer patients and survivors is also warranted.

2. **What are the effects of flavorants on the appeal and use of ENDS products, and what are their effects on smoking habits?** Research is needed to understand how the addition of characterizing and noncharacterizing flavors to ENDS affects youth and adult ENDS initiation, long-term use, dual use with combustible products, the likelihood that users will transition to combustible tobacco products, and the use and utility of ENDS as cessation devices.
3. **How do the marketing and availability of ENDS affect perception and use of ENDS as well as other tobacco products?** Concerns have been raised that ENDS use may undermine the progress that has been made in tobacco control by renormalizing cigarette smoking (82). Studies are needed to understand how the marketing and availability of ENDS influences the perception and use of these and other tobacco products, particularly among youth.
4. **How do tobacco control policies affect the pattern of ENDS use?** The ultimate effect of ENDS on public health will likely depend on how they are regulated. In places where ENDS use is encouraged as an alternative to combustible cigarettes, it is likely that ENDS use will be more commonplace. The consequences of such policies are unknown and need to be studied.

Understanding the potential role of ENDS for smoking cessation

1. **How do ENDS affect smoking reduction and cessation outcomes?** Among smokers, controlled clinical trials are needed to determine whether ENDS facilitate or hinder short- and long-term smoking cessation as well as whether use of ENDS in addition to combustible cigarettes undermines cessation efforts or increases nicotine addiction/dependence. Studies should consider outcomes for smokers interested and not interested in quitting smoking. Currently, there is insufficient evidence regarding the potential benefits or harms of ENDS use among cancer patients. Well-controlled trials examining the safety and efficacy of ENDS for treating tobacco dependence are needed to guide oncology practice guidelines.
2. **Can ENDS be used effectively in combination with existing FDA-approved cessation medications?** Patients who report poly-tobacco use or who use tobacco products in conjunction with NRT represent unique clinical challenges for appropriately managing acute nicotine withdrawal and preventing nicotine toxicity, particularly in medically vulnerable patients. On the other hand, given the marked acceptability of ENDS among cigarette smokers interested in quitting, clinical trials examining the safety and efficacy of combining ENDS with established FDA-approved cessation medications (standard of care) should be considered.
3. **How, if at all, should behavioral counseling be modified for ENDS cessation trials?** Clinical practice guidelines currently recommend delivery of behavioral counseling and pharmacotherapy for optimal cessation outcomes. Research examining varied behavioral protocols in combination with ENDS is also warranted.
4. **What effects does short- or long-term ENDS use have on smoking relapse among smokers who have quit using**

combustible cigarettes? The potential for abstinent smokers who sample ENDS to relapse to smoking as a result of nicotine or smoking cues triggered by ENDS should be evaluated, particularly in the context of stressful life events such as cancer diagnosis and treatment.

Policy Recommendations

As noted above, we lack data on the public health impact of ENDS on both individuals and the population as a whole, which makes it difficult to develop a comprehensive regulatory framework for these products at the current time. Nonetheless, it is prudent for policymakers to take steps to minimize the potential negative public health consequences of these products, particularly in youth, while taking care not to undermine their potential to reduce the harm caused by combustible cigarettes and other conventional tobacco products. The public health impact of cigarette smoking is devastating, and policy recommendations should consider reduction of the health hazards of smoking as paramount. With these goals in mind, AACR and ASCO make the following policy recommendations:

1. The AACR and ASCO support regulation of all ENDS that meet the statutory definition of tobacco products, as well as their component parts, by the FDA Center for Tobacco Products (CTP) using its authority under the Family Smoking Prevention and Tobacco Control Act (83). CTP should regulate both ENDS delivery systems and e-liquids containing tobacco-derived nicotine whether they are sold together or separately. The AACR and ASCO also support the major ENDS provisions in the FDA's proposed deeming regulation (21) that are outlined in Table 1, and we encourage the FDA to release the final rule in a timely manner. ENDS products that do not meet the statutory definition of tobacco products (including products containing synthetic nicotine) should be regulated by the FDA through other appropriate authorities.
2. ENDS manufacturers should be required to register with the FDA and report all product and ingredient listings, including harmful and potentially harmful components, as well as the nicotine concentration in the ENDS solution.
3. The AACR and ASCO encourage the FDA to exercise its regulatory authority to require health warning and safety labels in addition to the Agency's proposed nicotine warning on e-cigarette packaging and advertising as appropriate to protect the public health.
4. To prevent youth from initiating use of ENDS products, the AACR and ASCO encourage the FDA to restrict youth-oriented marketing of ENDS, including the following prohibitions:
 - i) self-service displays of ENDS in retail establishments;
 - ii) the provision of gifts and other giveaways with purchase of ENDS products;
 - iii) the sale and distribution of items such as hats or t-shirts with ENDS brand logos;
 - iv) brand name sponsorship of athletic, musical, or other social or cultural events, or of any team entry into those events; and
 - v) youth-oriented advertising of tobacco products, including the use of cartoon characters in tobacco product advertising, promotion, packaging, or labeling.

5. The AACR and ASCO support applying federal regulations to ENDS that would require Internet and other mail-order sellers of ENDS products to check the age and identification of customers at the point of purchase and delivery; to comply with all laws in the purchaser's state or local jurisdiction; and to pay all applicable federal, state, and local taxes.
6. The AACR and ASCO are concerned about the potential adverse health consequences of exposure to second- and third-hand ENDS aerosol. To protect the health of nonusers, we support prohibiting the use of ENDS in places where combustible tobacco product use is prohibited by federal, state, or local law until the safety of second- and third-hand aerosol exposure is established.
7. The AACR and ASCO fully support the FDA exercising its authority to require evidence-based changes to tobacco products and their constituents that are aimed at improving public health. Specifically, ASCO and the AACR support a product standard that would require all e-liquid refill bottles to be child proof, including childproof caps for eye-dropper refill bottles. Future research may point to the need for additional product changes for ENDS, including standards regulating design, constituents, nicotine levels, or other chemicals included in ENDS vapor.
8. Every effort should be made to prevent youth from using ENDS. Therefore, AACR and ASCO recommend a prohibition on ENDS and ENDS liquid containing candy and other youth-friendly flavors unless there is evidence demonstrating that these products do not encourage youth uptake of ENDS. Flavors or flavor names that are brand and/or trademarked names for candy, cookies, soda, ice cream, and other nontobacco products that are especially attractive or recognizable to youth should also be prohibited. Every effort should be made to prevent children from confusing ENDS and ENDS liquid with products designed for them or recognized as food. The AACR and ASCO recognize that flavored ENDS may be beneficial if they discourage the use of combustible products or facilitate cessation by appealing to the smoker who would use ENDS rather than cigarettes because of the flavoring. Today there is no evidence for or against this practice, and the public health benefits of flavored ENDS are currently unknown. Therefore, priority should be placed on preventing youth from using these products.
9. The AACR and ASCO urge policymakers to support research on ENDS, including in the areas identified in the research recommendations section of this policy statement. This research should be used to guide future federal, state, and local regulatory and policy decisions with regard to taxation, indoor e-cigarette use, flavorings and other product standards, and e-cigarette marketing, among other issues. Funding generated through tobacco product taxes, including any potential taxes levied on ENDS, should be used to help support research on ENDS and other tobacco products, but should not preclude the allocation of federal funding for this research.
10. The AACR and ASCO recommend full public disclosure of all data related to ENDS composition, use, and health effects for dissemination and independent review as well as to enhance policy decisions for ENDS product regulation.
11. Particularly in the absence of federal ENDS regulation, the AACR and ASCO encourage state and local governments to implement ENDS regulations within their authorities that are appropriate for protecting the public health, including restricting the sale, distribution, marketing, and advertising of ENDS to youth.
12. Evidence shows that increasing taxes on cigarettes has been one of the most effective tobacco control strategies (2) and differential taxation affects tobacco product use. The AACR and ASCO recommend taxing tobacco products proportionately to their harm. Therefore, at the present time, we recommend against taxing ENDS at equal or higher rates than combustible cigarettes.
13. The AACR and ASCO encourage international cooperation in developing standards for regulation of ENDS. Regulations should prioritize protection of the public's health and draw upon the best available scientific evidence whenever possible.

Summary

Rapid elimination of combustible tobacco products would dramatically reduce the burden of tobacco-related death and disease. The AACR and ASCO support every effort to reduce the use of combustible tobacco, and we support careful consideration of ENDS as potentially harmful, and potentially beneficial, products in this regard. The benefits and harms must be evaluated with respect to the population as a whole, taking into account the effect on youth, adults, nonsmokers, and smokers. There are currently too little data on the safety of ENDS and their efficacy as cessation products to recommend their use for the general population or for patients with chronic diseases such as cancer. The AACR and ASCO recommend strategic research into the composition, uptake, biologic effects, behavioral patterns, and health effects of ENDS use, including abuse liability of ENDS; research into how ENDS use affects other tobacco product use patterns; and research on how ENDS use affects treatment and outcomes for patients with cancer. The AACR and ASCO encourage policymakers to review the rapidly evolving literature regarding ENDS regularly and to make public health decisions based upon scientific evidence.

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Disclaimer

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