



HHS Public Access

Author manuscript

Circulation. Author manuscript; available in PMC 2020 November 05.

Published in final edited form as:

Circulation. 2014 October 14; 130(16): 1418–1436. doi:10.1161/CIR.000000000000107.

Electronic Cigarettes:

A Policy Statement From the American Heart Association

Aruni Bhatnagar [Director, Diabetes and Obesity Center, Smith and Lucille Gibson Professor,]

Division of Cardiovascular Medicine, University of Louisville, Co-Director, American Heart Association Tobacco Regulation and Addiction Center

Neal Benowitz [Professor of Medicine and Bioengineering & Therapeutic Sciences Chief,]

Division of Clinical Pharmacology University of California San Francisco

Chris Bullen [Director of the National Institute for Health Innovation and Associate Professor,]

School of Population Health, The University of Auckland, Auckland, New Zealand

Frank Chaloupka [Distinguished Professor,]

University of Illinois–Chicago

David Goff [Dean,]

Colorado School of Public Health

Timothy McAuley [Founder and Chief Executive Manager,]

Consulting for Health Air, Nature, & a Greener Environment, LLC (CHANGE)

Mariann R. Piano [Professor of Nursing and Interim Head,]

Department of Biobehavioral Health Science at the University of Illinois at Chicago College of Nursing

Rose Marie Robertson [American Heart Association Co-Director,]

American Heart Association Tobacco Regulation and Addiction Center

Kurt M. Ribisl [Professor,]

Health Behavior, University of North Carolina

Laurie P. Whitsel [Director of Policy Research,]

American Heart Association

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at http://www.heart.org/HEARTORG/General/Copyright-Permission-Guidelines_UCM_300404_Article.jsp. A link to the “Copyright Permissions Request Form” appears on the right side of the page.

This statement was approved by the American Heart Association Advocacy Coordinating Committee on July 28, 2014. A copy of the document is available at <http://my.americanheart.org/statements> by selecting either the “By Topic” link or the “By Publication Date” link. To purchase additional reprints, call 843-216-2533 or kelle.ramsay@wolterskluwer.com.

The American Heart Association requests that this document be cited as follows: Bhatnagar A, Whitsel LP, Ribisl KM, Bullen C, Chaloupka F, Piano MR, Robertson RM, McAuley T, Goff D, Benowitz N; on behalf of the American Heart Association Advocacy Coordinating Committee, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Electronic cigarettes: a policy statement from the American Heart Association. *Circulation*. 2014;130:1418–1436.

Maciej Goniewicz,
Roswell Park Cancer Institute

Steve A. Schroeder,
UCSF

Kenneth Warner,
University of Michigan

Rachel Widome
University of Minnesota

on behalf of the American Heart Association Advocacy Coordinating Committee, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research

Keywords

AHA Scientific Statements; cardiovascular disease; e-cigarettes; nicotine; public health; smoking; tobacco; tobacco smoke pollution

For decades, advocacy for tobacco control has been a priority of the American Heart Association (AHA). In partnership with major public health organizations, the association has made major strides in tobacco use prevention and cessation by prioritizing evidence-based strategies such as increasing excise taxes; passing comprehensive smoke-free air laws; facilitating US Food and Drug Administration (FDA) authority to regulate tobacco, including comprehensive tobacco cessation treatment within healthcare plans; and supporting adequate funding of comprehensive tobacco control programs in different states. These tobacco control efforts have cut in half the youth smoking rate from 1997 to 2007 and have saved >8 million lives in the past 50 years.¹ However, the work is far from done and has stalled, especially for people living below the poverty line, those with mental illnesses,² and those with low educational attainment.³ Unless current trends reverse, ≈5.6 million children alive today in the United States will die prematurely of smoking-related diseases.¹ Even now, cigarette smoking kills nearly half a million Americans each year, and an additional 16 million individuals suffer from smoking-related illness, which costs the United States \$289 billion dollars annually in direct medical care and other economic costs.¹

This statement reviews the latest science concerning one of the newest classes of products to enter the tobacco product landscape—electronic cigarettes (e-cigarettes), also called electronic nicotine delivery systems (ENDS)—and provides an overview on design, operations, constituents, toxicology, safety, user profiles, public health, youth access, impact as a cessation aid, and secondhand exposure. On the basis of the current evidence, we provide policy recommendations in key areas of tobacco control such as clean indoor air laws, taxation, regulation, preventing youth access, marketing and advertising to youth, counseling for cessation, surveillance, and defining e-cigarettes in state laws. The statement concludes by outlining a future research agenda to further our understanding of this emerging area of tobacco control and the impact of e-cigarettes on public health.

E-Cigarettes or ENDS

The first concept of an electric cigarette was patented in 1965 by Herbert A Gilbert.⁴ Subsequently, an aerosolized, high-frequency e-cigarette was patented in China by Mr. Hon Lik and Ruyan Technology; it entered the marketplace in 2003⁵ and was patented internationally in 2007.⁶ Ruyan has since registered patents in >40 countries, including the United States,⁷ and has already brought patent infringement lawsuits against several e-cigarette manufacturers.⁸ E-cigarette design and manufacturing processes continue to evolve, and most products on the market today use a simpler, battery-powered heating element instead of the high-frequency, ultrasonic technology patented by Ruyan.⁷

As of early 2014, there were 466 brands and 7764 unique flavors of e-cigarette products.⁹ These products are now widely available online¹⁰ and in retail outlets in many countries across the world.^{11,12} In contrast to combustible products, e-cigarette availability in retail outlets in the United States is currently more likely in neighborhoods with higher median household income and a lower percentage of black and Hispanic residents.¹² E-cigarette availability in retail outlets is also higher in states with weak or nonexistent laws for clean indoor air and low cigarette taxes.¹²

Although the sale of e-cigarettes is prohibited in some countries (Australia, Brazil, Canada, Mexico, Panama, Singapore, and Switzerland), it is allowed in most others, including the United States.¹³ The number of e-cigarettes sold has increased exponentially year by year. Wells Fargo has predicted that sales margins for e-cigarettes could grow to \$10 billion by 2017, surpassing conventional cigarette sales margins.¹⁴ The big 3 major tobacco companies have been purchasing independent e-cigarette companies and may share 75% of the profit pool in 10 years.¹⁴

E-cigarettes are battery-powered devices that have cartridges or refillable tanks containing a liquid mixture composed primarily of propylene glycol and/or glycerol and nicotine, as well as flavorings and other chemicals.⁵ During use, inhalation activates a pressure-sensitive circuit that heats the atomizer and turns the liquid into an aerosol that is inhaled by the user through the mouthpiece and exhaled as a fine mist.⁵ Some e-cigarettes have buttons that allow the user to manually activate the heating element. The exhaled aerosol does not contain smoke, tar, or carbon monoxide. Studies of specific types of e-cigarettes have shown that compared with conventional cigarettes, the byproducts from their aerosols produce very low levels of air toxins.^{15–17} Proponents of e-cigarettes maintain that these products emulate smoking behavior without exposing the user to the toxic smoke constituents of conventional cigarettes that are deleterious to health, so there would be a public health benefit if individual smokers completely switched or substantially reduced their cigarette smoking habit.^{18–20} However, the use of e-cigarettes could be a problem at the population level. For instance, e-cigarettes could fuel and promote nicotine addiction, especially in children, and their acceptance has the potential to renormalize smoking behavior. E-cigarette use could also potentially serve as a gateway to other drugs and harmful substances.²¹

E-Cigarettes: Design and Operation

Since their initial manufacturing in 2003, there has been a rapid growth and evolution in the types, design, and overall engineering characteristics of e-cigarettes.^{22,23} This has resulted in a large degree of product variability in size, potential nicotine concentrations, and e-liquid formulations. There have also been changes in electrical circuitry (eg, heating element or atomizer) and battery life that allow for more e-liquid delivery, adjustments in flavor, and longer device use.

Different types of e-cigarettes are being developed continuously. Table 1 lists some of the different e-cigarette types and name brands on the market today. Newer second- and third-generation devices allow for multiple types of user customization. This has resulted in cross-product and within-product differences in aerosol production, nicotine delivery, and product use risk.²² These developments significantly complicate the ability to assess the impact of e-cigarettes on individual and population health.^{22,23}

Regardless of type, there are 3 basic e-cigarette components: a battery, an e-liquid-containing cartridge, and an atomizer (ie, a vaporization chamber with heating element).²¹ Other components include an airflow sensor (sensing inhalation), a microchip for controlling the heating element, and a light-emitting diode light at the tip that simulates a burning cigarette tip.²¹ All devices have air holes, which control the pressure drop and facilitate the flow of air required for puffing.²² E-cigarettes are available with automatic or manual button-activated batteries. The battery in an automatic device is activated by inhalation or the drag, whereas manual devices require the depression of a button for battery activation.²² The smokelike aerosol produced by these devices is not because of the combustion of organic material; rather, it is an aerosol of the e-liquid. As noted, the “atomizers” contain the heating elements that convert the fluid into an aerosol. Such atomizers are an essential component of all vaporizers, and they consist of a small heating element that evaporates the fluid and a wicking device that draws in the fluid. Since the inception of e-cigarettes, the atomizers have undergone dramatic engineering changes. Developments include the evolution of the atomizer into “cartomizers” (cartridge plus atomizer), which is a combination of an e-liquid distribution system and a wick/fiber and heating element.²³

Second- and third-generation e-cigarettes models, which are larger than the first “cigarette-like” e-cigarettes (cigalikes), are referred to as “clearomizers,” “tankomizers,” or “carotanks” because they can hold several milliliters of fluid in refillable reservoirs. Some second- and third-generation e-cigarette batteries are available in different voltages (3.0 to 7.0 V) and with greater battery life (greater milliampere-hour) than earlier models. Within the atomizer, a resistance wire is encircled around the wicking device that draws the fluid in. When activated by the sensing device, the resistance wire rapidly heats up, turning the fluid into an aerosol, which is then inhaled by the user. The resistance and voltage applied to the heating element, as well as the material from which the heating element is made, are important determinants of the temperature achieved, which determines in part the amount and quality of the aerosol produced by the atomizer.

Some second- and third-generation e-cigarettes have programmed pumps, diaphragms, or micropumps on microelec-tromechanical systems. These allow for a specific programmed amount or a combination of e-liquid delivery to the aerosol generator.²² Some e-cigarettes contain programmable logic units, integrated circuits, and other electronic components that are used to display average use cycle and safety warnings.²² Ongoing product development and evolution are likely to continue, and therefore, new regulatory policies will be important to ensure appropriate quality control.

Profile of Users

The number and duration of surveys are increasing and variably include current, former, and nonsmoker categories.^{24,25} These surveys are difficult to consolidate because they have been undertaken in different populations and jurisdictions, using different sampling methods and definitions, over a number of years while e-cigarette types, visibility, and use have increased dramatically. Generally, non-Hispanic whites, current smokers, young adults, and those with a higher education and higher income perceive e-cigarettes as less harmful than combustible tobacco products and are more likely to use them.^{24,26–29} European and North American surveys conducted in 2012 and 2013 report that most e-cigarette users are current or former smokers³⁰; 40% to 70% of all adults have heard about them, with awareness highest in smokers and growing.^{26,31–33} Such surveys also report that $\approx 3\%$ to 7% of the adult population has ever used e-cigarettes^{26,34} Among smokers in the United States and Great Britain, $\approx 11\%$ report ever having used e-cigarettes, whereas the use of e-cigarettes is significantly lower (0.5% – 1.0%) in nonsmokers.^{25,26,35} A study conducted in the Czech Republic in 2012 revealed that almost 20% of smokers who try e-cigarettes go on to become regular users.³⁶

It is uncertain how many e-cigarette users are smokers who really want to stop cigarette smoking or ex-smokers but persistent e-cigarette users, or who want to be dual users. At present, there are few longitudinal studies to assess how many smokers are able to completely quit cigarette use, whether they continue e-cigarette use after quitting or whether they continue dual use, that is, using them concurrently with combustible products.³⁶ Epidemiological studies and population surveys also indicate that although many e-cigarette users plan to use the devices to quit or reduce their smoking, they are usually using them in a dual-use capacity, especially in places where smoking is restricted.^{35–40} A survey conducted in 2012 showed that $>80\%$ of current e-cigarette users do not use them on a daily basis, and almost half of all smokers indicated they may use e-cigarettes in the future.³⁵ Finally, among college students, another e-cigarette user group, e-cigarette use may not be motivated by the desire to quit smoking, nor may it lead to quitting.⁴¹ In conclusion, the overall use patterns are unclear and constantly changing, which makes it difficult to draw firm conclusions about the prevalence, preference, and purpose of e-cigarette use.

Youth

Concerned public health advocates see e-cigarettes as a route to nicotine addiction and possibly as a potential gateway to tobacco use in youth or nonsmokers and to reinitiation of tobacco product use by former users.⁴² Data from the 2011 to 2012 National Youth Tobacco

Survey⁴³ showed that among students in grades 6 through 12, current e-cigarette use (1 day in the past 30 days) increased from 1.1% in 2011 to 2.1% in 2012 and any use of e-cigarettes (ever use) increased from 3.3% to 6.8% in the same corresponding years. Overall, by 2012, 1.78 million high school and middle school students nationwide had tried e-cigarettes. For those students who had ever used e-cigarettes, 9.3% reported never smoking conventional cigarettes, whereas 76.3% of current e-cigarette users responded that they also smoke conventional cigarettes. Among never-smokers, 0.7% were currently users (past 30 days), which indicates that few never-smokers who try e-cigarettes continue their use.⁴⁴ A survey of 40 000 middle school and high school students from ≈200 schools has shown that e-cigarette use is higher in current smokers and ever-smokers and among those intending to quit.⁴³ This surveillance does not address whether adolescents are using e-cigarettes as a gateway to smoking cigarettes, but adolescents do consider e-cigarettes as high-tech, accessible, and convenient, especially in places where smoking cigarettes is not allowed.⁴⁵ Increasingly, there is robust marketing and advertising using celebrities and appealing flavors (eg, chocolate, strawberry, and vanilla) to make e-cigarettes especially more attractive and appealing to children and adolescents.⁴⁵ Much of the marketing for e-cigarettes has been through the Internet and social media outlets such as YouTube,⁴⁶ but increasingly, e-cigarettes are advertised on television, radio, and in the print media, where broadcast cigarette ads have been banned since 1971.⁴⁷ Data from a US population survey indicated that for those reporting they have heard about e-cigarettes, the majority (48%) reported television as their primary source, followed by “in-person conversation” and the Internet.³⁵ Another study found that youth exposure to television advertisements for e-cigarettes increased 256% between 2011 and 2013, with 24 million youth reached.⁴⁸ Online searches for e-cigarettes have surpassed those for nicotine replacement therapies (NRTs) and snus, products that have been on the market much longer.⁴⁹

E-Cigarettes and Public Health

The major public health issues regarding e-cigarettes include whether or not they may contribute to reducing overall tobacco-related harm through complete cessation or possibly through reduction of the number of cigarettes smoked, denormalization of smoking, reduction in prevalence of use of combustible products (especially cigarettes), reduction of second-hand smoke exposure, and diminishing the influence of the tobacco industry. Although some believe that acceptance of e-cigarettes has the potential to reverse the social norm for prohibiting smoking in public places achieved over decades of advocacy work, others see these products as a way to denormalize smoking because they are a potential mechanism for quitting.²⁰ It is not known whether the emerging e-cigarette technology will shift people from combustible products to the exclusive use of e-cigarettes or whether dual use will persist.⁵⁰

E-Cigarettes as a Cessation Aid

Current evidence evaluating the efficacy of these products as a cessation aid is sparse, confined to 2 randomized controlled trials and 1 large cross-sectional study, anecdotal reports, and Internet-based surveys. A large cross-sectional study showed that smokers who wanted to quit without professional help were significantly more likely to report abstinence

using e-cigarettes than with traditional cessation aids or going “cold turkey.”⁵¹ The adjusted odds ratio for self-reported cigarette abstinence in e-cigarette users was 1.63 (95% confidence interval 1.17–2.27) higher than with NRT use and 1.61 (95% confidence interval 1.19–2.18) higher than for those using no aid. In a survey in the United Kingdom, 67.8% of e-cigarette users “completely replaced tobacco cigarettes with electronic cigarettes”; however, these reports are confounded by a self-selection bias in that the respondents are often e-cigarette enthusiasts.³⁹ In contrast, other surveys suggest that compared with never-users, e-cigarette users are less likely to be tobacco abstinent⁵² and that e-cigarette users were no more likely than cigarette smokers to have quit permanently despite having reduced their cigarette consumption.²⁴

The largest randomized controlled trial conducted to date, which used e-cigarettes available on the market in 2010 that are now obsolete, had cartridges labeled as containing 16 mg of nicotine and showed that the study e-cigarettes were modestly effective with or without nicotine at helping smokers quit, on par with the abstinence achieved with nicotine patches.⁵³ At 6 months, the verified quit rates were 7.3% with nicotine e-cigarettes, 5.8% with nicotine patch, and 4.1% with placebo e-cigarette treatment. This study also found that dual use persisted at 6 months at moderately high levels (approximately one third of participants); dual use also occurred with patch users but at much lower levels (7%).

Health Effects and Safety

The overall health effects of e-cigarettes should be considered both in the context of the intrinsic toxicity of e-cigarettes and with regard to their relative toxicity compared with the well-known injurious effects of smoking conventional cigarettes. Even if there are some intrinsic adverse health effects of e-cigarettes, there would be a public health benefit if e-cigarettes proved to be much less hazardous than combustible cigarettes and if smokers could switch entirely from conventional cigarettes to e-cigarettes. However, in general, the health effects of e-cigarettes have not been well studied, and the potential harm incurred by long-term use of these devices remains completely unknown. Nevertheless, some studies have examined the health effects of e-cigarettes by considering the constituents of their aerosol and their known toxicities and through toxicological evaluation of e-cigarette liquids and aerosols. Current data from human exposures, including experimental studies, and surveys of adverse effects and accidental exposure are discussed below. Available data on the safety and health effects of e-cigarettes have been reviewed elsewhere.^{54–56}

The constituent and toxicant levels within the e-liquid and aerosol vary depending on the type of e-liquid (or e-juice) formulation and the specific design of the device.⁵⁷ Typically, e-liquid formulations contain nicotine, flavors, water, glycerin, and propylene glycol.⁵⁷ Exposure to levels and types of metals or other materials within the aerosol depends on the material and other engineering features of the heating coils.⁵⁷ Potential metallic and nanoparticles derived from the heating coils can include tin, iron, nickel, and chromium.^{22,58} Other materials in e-cigarettes could include ceramics, plastics, rubber, filament fibers, and foams. Some of these materials can be aerosolized and inhaled. Importantly, low levels of harmful or potentially harmful metals such as lead, nickel, and chromium are listed as having been detected.^{22,59} The e-liquids typically contain many flavorings, including

tobacco flavoring. In tobacco-flavored products, other tobacco “contaminants” may be present. Trace levels of tobacco-specific *N*-nitrosamines, polycyclic aromatic hydrocarbons, and volatile organic compounds in the e-liquid and vapor have been reported; however, the amounts are deemed too low to cause human risk.^{57,60} Other flavorings include fruit and spices (eg, strawberry, black cherry, and Ceylon cinnamon) or flavorings such as “bubble gum” or “chocolate truffle.”

Propylene glycol is a major ingredient in e-cigarettes. It is approved by the FDA as a solubilizing agent for different types of medications and is considered generally nontoxic.⁵⁹ However, in 1 product, small amounts of diethylene glycol, a potential byproduct of nonpharmaceutical grade propylene glycol, have been detected.⁶¹ Other contaminants found in particular products have included the weight-loss chemical rimonabant (Zimulti) and the erectile dysfunction medication tadalafil (the active ingredient in Cialis). As a result, the FDA has issued warnings to several e-cigarette companies for selling e-cartridges with these contaminants.⁶¹

Nicotine

Nicotine is delivered by most but not all e-cigarette products. Most e-liquids contain 24 mg/mL, 18 mg/mL, 12 mg/mL, or 6 mg/mL nicotine and are qualified by the manufacturers as high, medium, or low nicotine strength.⁶² Some e-liquids are available in 36 mg/mL concentrations.⁶² Nicotine solutions of 100 mg/mL for use in making e-cigarette refill liquids are available over the Internet. As a point of context, 1 regular cigarette contains ≈10 to 15 mg of nicotine and delivers a systemic dose of ≈1 mg of nicotine. Testing has revealed that the nicotine content noted in some e-cigarette products and refill solutions has been incorrect and either overestimates or underestimates the amount of nicotine,⁶¹ which indicates a need for regulatory oversight.⁶¹ The overall total amount of nicotine in the e-liquid depends on the size of the refill vial; for example, a 10-mL bottle of 24 mg/mL contains a total of 240 mg of nicotine.

Blood levels of nicotine are generally lower from e-cigarette use than from conventional cigarettes, but users of some e-cigarette tank systems with more powerful batteries that heat liquids to higher temperatures may achieve blood nicotine levels comparable to those of cigarette smokers.^{63,64} The extent to which nicotine inhaled from an e-cigarette is absorbed through the lungs or via the throat and upper airway has not been determined. The size distribution of particles generated by e-cigarettes, discussed later in this report, suggests that at least some pulmonary absorption is likely. In 1 study,⁵⁸ it was found that absorption of nicotine from e-cigarettes was lower than from tobacco cigarettes even with the new-generation cartomizers, which suggests that most absorption from the devices occurs in the buccal mucosa or upper airways. Compared with smoking 1 tobacco cigarette, the electronic devices and liquid used in this study delivered one third to one fourth the amount of nicotine after 5 minutes of use. New-generation e-cigarette devices were more efficient in nicotine delivery but still delivered nicotine much more slowly than tobacco cigarettes.

The main health concern for nicotine in cigarette smokers is maintenance of addiction. Most of the adverse health effects of smoking are caused by tobacco combustion products,⁶⁵ but there are some health concerns that are related to nicotine per se. Many of these concerns are

related to the ability of nicotine to release catecholamines, including hemodynamic effects (increase in heart rate, a transient increase in blood pressure, vasoconstriction of coronary and other vascular beds), adverse effects on lipids, and induction of insulin resistance.⁶⁵ Nicotine has also been reported to produce endothelial dysfunction and to cause fetal teratogenicity, operating by different mechanisms.⁶⁶ Nicotine in vitro and in animals can inhibit apoptosis and enhance angiogenesis, effects that raise concerns about a role of nicotine in promoting the development and spread of cancer and in the acceleration of atherosclerotic disease.⁶⁷

Because most people use nicotine in the form of tobacco products, there are relatively few data on the health effects of prolonged exposure to pure nicotine. There are some studies of prolonged NRT in smokers who have quit smoking.^{68,69} In these studies, no adverse effects have been found when nicotine medication was administered for months to several years. Other studies indicate that patients with known cardiovascular disease tolerate NRT well for periods up to 12 weeks.⁶⁵

Because most of the toxicity from cigarette smoking derives from combustion products, the health effects of smokeless tobacco could be examined to assess potential long-term adverse effects of nicotine without exposure to combustion products. Smokeless tobacco users take in as much nicotine as cigarette smokers, although not by the pulmonary route.⁷⁰ The most extensive and rigorous epidemiological studies on smokeless tobacco use come from Scandinavia, where a large percentage of men use snus, a smokeless tobacco product that contains nicotine but relatively low levels of carcinogens and other toxins. These studies report only a very small cardiovascular disease risk in snus users compared with tobacco smokers.⁷¹ However, discontinuation of snus use after MI has been found to be associated with nearly halved mortality risk, which is similar in magnitude to the benefit associated with smoking cessation.⁷² Thus, although the adverse health effects of e-cigarettes are not known, they are likely to be much less than those of cigarette smoking, but could be significant in individuals with heart disease.

Acute nicotine toxicity is a concern if e-cigarette liquids are ingested, which may occur accidentally by children or intentionally by adults as a suicidal overdose, or with dermal exposure. Nicotine is well absorbed through the skin when in an alkaline solution, and e-cigarette liquids are alkaline. Nicotine intoxication commonly causes dizziness, nausea, vomiting, pallor, tachycardia, and sweating. Abdominal pain, salivation, lacrimation, and diarrhea have also been noted. Confusion, agitation, lethargy, convulsions, and possibly death are seen in cases of severe poisonings that cause hypotension and respiratory muscle weakness.⁷³ In such cases, respiratory arrest is the most likely the cause of death.⁷³ Symptoms usually begin within 15 minutes of acute liquid nicotine exposure and resolve within 1 to 2 hours.⁷³ Cutaneous exposure may lead to delayed onset and prolonged symptoms. A number of cases of accidental exposure in children and adults have been reported by poison control centers.^{74,75} The concentrations of nicotine in e-cigarette liquids are high enough to be fatal to a child if even a few milliliters is ingested.^{76,77} There are isolated reports of severe toxicity, including death, in children who ingested e-cigarette liquids. Nationally, calls to poison control centers attributable to accidental exposure to e-

cigarettes have increased dramatically (161%–333%), mostly involving children who were exposed to the replacement cartridges and liquids containing nicotine.^{78,79}

Minor Tobacco Alkaloids and Tobacco-Specific Nitrosamines

Some but not all e-cigarette liquids contain minor tobacco alkaloids (such as nornicotine, anabasine, or anatabine) and tobacco-specific nitrosamines, such as *N*'-nitrosonornicotine and 4-(methylnitrosamine)-1-(3-pyridyl)-1-butanone (NNK).⁷⁶ These may be present in the liquids because nicotine is extracted from tobacco, and these compounds are present in tobacco. Several minor tobacco alkaloids have nicotine-like actions, although they are less potent than nicotine. Extensive evidence has shown that tobacco-specific nitrosamines are highly carcinogenic⁸⁰; however, the levels of both minor alkaloids and nitrosamines present in most e-cigarette products are low and are unlikely to pose a significant human health risk.⁸¹ Minor alkaloids and tobacco-specific nitrosamine are undetectable in nicotine medications.⁸²

Carbonyls and Other Volatile Chemicals

Thermal degradation of propylene glycol can generate propylene oxide, which is classified by the International Agency for Research on Cancer as a class 2B carcinogen. The heating of glycerol can form acrolein, which is an irritant and oxidizing agent thought to contribute to adverse pulmonary and cardiovascular effects of cigarette smoking.^{83–85} Analyses of emissions from cigarettes have found primarily formaldehyde, acetaldehyde, and acrolein, along with low levels of toluene, xylene, benzene, and butadiene.⁸⁶ Although these compounds are potentially toxic, the levels in e-cigarette emissions are many-fold lower than those found in cigarette smoke and in some cases similar to those found in the mist of medicinal nicotine inhalers. The risk of exposure to low levels of these compounds is unknown. With intense heating, such as from the use of tank models with large batteries, higher amounts of formaldehyde are generated, in some cases similar to levels found in cigarettes smoke.^{60,87} Formaldehyde is a carcinogen and an irritant, but the risks of prolonged inhalation of formaldehyde at the levels found in e-cigarette aerosols are unknown.

Propylene glycol and glycerol are added in e-cigarette liquids to generate an aerosol that resembles cigarette smoke. Animal studies of propylene glycol inhalation for up to several months have revealed little or no toxicity.^{88,89} Propylene glycol is used to generate theater fog and is used in aviation industries. It can cause eye and respiratory irritation, and there have been concerns about respiratory irritation in the theater.⁹⁰ Thus, there are concerns about potential harm from the inhalation of propylene glycol from e-cigarettes, particularly for people with asthma or chronic obstructive lung disease, although there is little research on the effects in susceptible populations.

Metals

Detectable levels of metals such as tin, silver, iron, nickel, cadmium, and copper have been detected in some but not all e-cigarettes in which they could be generated from the heating element.⁵⁸ Some e-cigarette solutions contain tin “whiskers,” microscopic crystals that emanate from tin in the solder joints.⁵⁸ The nature and amount of metals generated depend

on the design of the e-cigarette product, and some generate few or no metals. The levels of metals in e-cigarette emission are generally low, but little is known about the toxicity of prolonged inhalation of low levels of metals.

Particles

E-cigarettes generate an aerosol that consists of fine and ultrafine particles in a gas phase. These particles are likely generated from supersaturated 1,2-propanediol vapor. Nanoparticles present in some e-cigarette aerosols have been reported also to contain trace levels of tin, chromium, and nickel.⁵⁸ It has been reported that particle number concentration of the mainstream aerosol generated by e-cigarettes, averaged across several liquids and types of e-cigarettes, was similar to that of conventional tobacco cigarettes.^{91,92} The number of particles in e-cigarette aerosol has been found to be influenced by the liquid nicotine content and puffing time, and higher levels of particles were generated by e-cigarettes that contained higher nicotine concentrations.⁹¹ The particle size distribution from the few e-cigarette devices that have been tested has been reported to be similar to that of conventional cigarettes.⁹² Particles such as those generated by e-cigarettes can reach deep into the lungs and potentially cross into the systemic circulation. Carbonaceous particles present in cigarette smoke and ambient air have been demonstrated to have adverse cardiovascular and respiratory effects in both human and animal models.^{93,94} It is not known whether the type of particles generated by e-cigarettes have the same toxicity as particles present in ambient air or those generated by conventional cigarettes, but this is an important question for determining the long-term safety of e-cigarettes.

Toxicology Studies

Results of several toxicology studies with e-cigarette liquids and aerosols have been published. These studies show that e-cigarette liquids and aerosols affect the viability of established cultured cell lines, such as human or mouse fibroblasts, human embryonic stem cells, mouse neural stem cells, and cardiomyoblasts.^{95–97} For example, using 3 different cell types (ie, human embryonic stem cells, mouse-derived neural stem cells, and human pulmonary fibroblasts), Bahl et al⁹⁵ examined the cytotoxicity of several flavored e-cigarette refill extracts from 4 different manufacturers. They reported that extract flavorings such as Ceylon cinnamon were toxic to all 3 cell types tested. In addition, 1 butterscotch sample was highly toxic, whereas 2 other butterscotch samples from the same company had low toxicity, which shows the within-product and between-product variability.⁹⁵ Overall, the human embryonic and neonatal mouse-derived stem cells were more sensitive than adult lung fibroblasts to the cytotoxic effects of the extracts. Cytotoxicity was not caused by nicotine but was correlated with the number and concentrations of flavoring chemicals. In general, cytotoxicity appeared to be related to the concentrations and numbers of flavorings used and unrelated to nicotine. Of particular concern with respect to cytotoxicity of flavorings are the effects of cinnamaldehyde, a flavoring that is approved for use in food but can be dangerous when inhaled.⁹⁸ Aerosols of some but not all e-cigarettes have also been reported to be mildly cytotoxic.⁹⁸

Although the nature, concentration, and time course of exposure to e-cigarette constituents are likely to be quite different from those present in tobacco cigarette smoke, in general, the

few studies conducted so far suggest that e-cigarette emissions are much less toxic than cigarette smoke in cytotoxicity tests. The significance of these findings to the in vivo toxicity of e-cigarette liquid constituents is not clear, and additional research is needed to establish the potential toxicity of flavors and other e-cigarette constituents.

Human Health Effects

To date, relatively little research has been conducted on the human health effects of e-cigarettes. Spontaneous reports and clinical trial data have reported common minor side effects of throat and mouth irritation, dry cough, nausea, and vomiting. No serious adverse effects have been reported in clinical trials with >6 months of use compared with nicotine patches, with no difference between groups.^{53,99} Because propylene glycol as a constituent of theater fog is known to cause respiratory irritation, pulmonary toxicity has been a reasonable concern. One study of 10 healthy smokers using 1 brand of e-cigarette (Nobacco, 11 mg of nicotine, >60% propylene glycol) as desired for 5 minutes found no significant effect on conventional spirometry measures but did find a small but significant increase in dynamic airway resistance (18%) and a significant decrease in exhaled nitric oxide (16%).¹⁰⁰ Smokers in this study had abstained from cigarette smoking for only 4 hours before using e-cigarettes, and there was no comparison with the effects of a conventional cigarette. Another study examined pulmonary function in 15 cigarette smokers and 15 never-smokers who used the same brand of e-cigarette (60% propylene glycol, 11 mg of nicotine).¹⁰¹ Cigarette smoking caused a significant decrease in forced expiratory volume in the first second of expiration/forced vital capacity (FEV₁/FVC), which was not seen with e-cigarette use. This study also reported that cigarette smoking increased white blood cell count, which reflects an inflammatory response, whereas there was no significant change with the use of e-cigarettes.¹⁰¹ A small retrospective study of pulmonary function and symptoms in smokers with asthma who switched to e-cigarettes found no adverse effects of e-cigarettes, but rather, the e-cigarette users had improved pulmonary function and reduced severity of asthma symptoms.¹⁰² Eighteen heavy smokers with mild to moderate asthma who were taking a stable dose of inhaled corticosteroids and long-acting β -agonists had pulmonary function tests before and 6 and 12 months after beginning e-cigarette use. These individuals mostly started with e-cigarettes that were cigarette-like, but most switched later to tank-type devices. Ten individuals quit smoking entirely, whereas 8 continued dual use. Dual users decreased their number of cigarettes smoked per day from an average of 22.4 at baseline to 3.9 per day at 12 months. These subjects showed a small but significant improvement in FEV₁ and forced mid-expiratory flow (25%–75%) and reduced airway responsiveness to inhaled methacholine, as well as an improved score on an asthma control questionnaire. The authors comment that the improvement in asthma symptoms may be related to stopping smoking or smoking fewer cigarettes, which could have led to less severe inflammation or a reduction in corticosteroid insensitivity. Although it was small, retrospective, and not controlled, this study does provide evidence that e-cigarette use is not harmful to people with mild to moderate asthma, but more extensive studies are required to establish the safety of e-cigarette use in this population.

Few studies have reported the cardiovascular effects of e-cigarettes. The results of these studies suggest that e-cigarettes can increase heart rate and blood pressure, as expected with

systemic absorption in nicotine. The use of e-cigarettes for 7 minutes did not cause diastolic dysfunction, which was seen with conventional cigarette smoking.⁵⁵ Another study found that e-cigarette use had no effect on flow velocity reserve of the left anterior descending coronary artery assessed by echo-cardiography, whereas cigarette smoking caused a decline in flow reserve (16%) and an increase in coronary vascular resistance (19%).⁵⁵ A case of atrial fibrillation in an elderly person after e-cigarette use has been reported, an effect that could have been caused by the autonomic nervous system effects of nicotine.¹⁰³ One case of lipid pneumonia has been reported in an e-cigarette user, but the causation is questionable because there is no clear biological plausibility.¹⁰²

In summary, the data on health effects to date, studied primarily in healthy people with short-term exposure, reveal little or no evidence of severe adverse events. Respiratory irritation and the bronchial constriction from a propylene glycol aerosol raise concerns about harm to people with asthma and chronic obstructive pulmonary disease, but 1 small study reports no harm but rather benefit when users quit smoking or smoke fewer cigarettes per day. There are no reports of e-cigarette safety in patients with known cardiovascular disease.

Secondhand E-Cigarette Aerosol Exposure

Passive cigarette smoke exposure is hazardous. It is associated with an increased risk of respiratory disease, including asthma; a variety of infectious diseases; lung cancer; acute coronary events; and stroke.¹⁰⁴ Acute exposure to secondhand smoke produces endothelial dysfunction and platelet activation. Most or all of the acute adverse effects of secondhand smoke are thought to result from exposure to the combustion products of tobacco, including many oxidants and other reactive chemicals.

Most of the secondhand smoke generated from conventional cigarettes results from sidestream smoke, which accounts for 75% of the burning cigarette mass. E-cigarettes do not generate sidestream aerosol. The secondhand emissions from e-cigarettes consist entirely of what is exhaled after inhalation by the user. We focus on data from studies in which aerosol generated by e-cigarette users was evaluated.

Schripp et al¹⁰⁵ studied secondhand emissions by asking a volunteer to use e-cigarettes in a closed chamber. Analysis of the air revealed the presence of formaldehyde, acrolein, isoprene, acetaldehyde, and acetic acid, but at levels 5 to 40 times lower than those generated by a combusted cigarette. Schober et al¹⁰⁶ conducted 6 sessions, each of which consisted of 3 subjects using e-cigarettes as desired for 2 hours in a 45-m³ ventilated room. The e-cigarettes were refillable tank devices with a liquid that contained both propylene glycol and glycerin and either 22 mg of nicotine per milliliter or zero nicotine. E-cigarette use significantly increased PM_{2.5} (particulate matter <2.5 μm in size), propylene glycol, glycerin, and nicotine, but not formaldehyde, benzene, acrolein, or acetone. There was a 30% to 90% increase in the sum of 16 measured polycyclic aromatic hydrocarbons and a 2.4-fold increase in ambient aluminum concentration. No comparisons were made to secondhand cigarette smoke. Czogala et al¹⁷ compared ambient levels of nicotine in a ventilated room in which people had either smoked conventional cigarettes or used e-cigarettes. Five subjects generated the aerosol over 1 hour using either pen or tank-type e-cigarettes. With e-cigarette use, the ambient level of nicotine was ≈10% of that seen with

smoking conventional cigarettes (3.3 versus 31.6 $\mu\text{g}/\text{m}^3$). The ambient $\text{PM}_{2.5}$ concentration after e-cigarette use was $\approx 18\%$ of that seen with cigarette smoking. In another study by Flouris et al,¹⁰¹ 15 nonsmokers were exposed in a 60- m^3 ventilated chamber to 1 hour of secondhand cigarette smoke (at a concentration simulating that of a smoky bar) or to e-cigarette aerosol generated by a smoking machine. The study found that serum cotinine was similar in nonsmokers after secondhand tobacco smoke and e-cigarette aerosol exposure (2.6 versus 2.4 ng/mL). Exposure to e-cigarette aerosol had no effect on pulmonary function or white blood cell count. Thus, secondhand exposure to e-cigarette aerosol exposes a nonsmoker to nicotine, particulates, and several potentially toxic organic chemicals, but at much lower levels than from conventional cigarette smoke. The biological effects of such an exposure are expected to be much less than that of secondhand smoke, but nonsmokers are exposed to some nicotine, and the regular use of e-cigarettes has the potential to substantially contaminate the environment with nicotine.

Policy Guidance

Summary Position

The AHA recognizes the increase in e-cigarette use and the need to develop a clear policy position on their use and their impact on the tobacco control movement. E-cigarettes either do not contain or have lower levels of several tobacco-derived harmful and potentially harmful constituents compared with cigarettes and smokeless tobacco. In comparison with NRTs, e-cigarette use has increased at an unprecedented rate, which presents an opportunity for harm reduction if smokers use them as substitutes for cigarettes. However, although firm evidence is lacking, there are concerns that e-cigarette use and acceptance of e-cigarettes has the potential to renormalize smoking behavior, sustain dual use, and initiate or maintain nicotine addiction. Their use also could serve as a gateway to reinitiation of smoking by ex-smokers. Unregulated e-cigarette use also has the potential to erode gains in smoking cessation and smoke-free laws. The AHA considers e-cigarettes that contain nicotine to be tobacco products and therefore supports their regulation under existing laws relating to the use and marketing of tobacco products. To prevent the potential negative public health impact of e-cigarettes, we strongly support laws and regulation that prohibit the sale and marketing of e-cigarettes to youth. We support effective regulation that addresses marketing, labeling, quality control of manufacturing, and standards for contaminants. We also support the inclusion of e-cigarettes in smoke-free air laws. Moreover, we consider it important to monitor and prevent these products from serving as gateway products or as an initiation to nicotine addiction in nonsmokers and reinitiation in smokers. We will continue to assess the scientific evidence relating to their long-term health effects and their efficacy as a smoking cessation aid and encourage the development of a robust research agenda to understand the public health impact of e-cigarettes, especially in at-risk populations.

Below, we summarize the association's current policy guidance on specific issues related to tobacco control, as well as the rationale underlying the policy recommendation. This policy guidance was developed by an expert advisory group and leading researchers in the field of tobacco control and prevention and e-cigarettes, in tandem with a comprehensive review of

the literature. The association's policy guidance will continue to be updated as rapidly evolving evidence emerges.

Inclusion of E-Cigarettes in Smoke-Free Air Laws

The AHA supports the inclusion of e-cigarettes in smoke-free air laws.

Although the levels of toxic constituents in e-cigarette aerosol are much lower than those in cigarette smoke,¹⁵ there is still some level of passive exposure to organic compounds, nicotine, and fine particles.^{58,105,107} To date, there is insufficient evidence to support the notion that exposure to exhaled aerosol has a deleterious impact on bystanders.²⁶ Some studies have found very low concentrations of air pollutants across different types, liquids, puff durations, and nicotine concentrations.^{15,105} The levels of particle and nicotine exposure vary with the composition of the liquids, the type of e-cigarette, size of the room, puff duration, interval between puffs, and the number of users.¹⁰⁵ Nevertheless, there is concern that nonsmokers will be involuntarily exposed to nicotine, which could be substantial where there is heavy e-cigarette use in confined spaces. Moreover, unregulated e-cigarette use has the potential to recreate a social norm around tobacco product use in public places,^{108–110} unraveling decades of work on comprehensive smoke-free air laws. It is not always easy to identify that a person is using an e-cigarette, because there is not the large plume of smoke or the strong detectable odor that comes from conventional cigarettes. Therefore, the use of e-cigarettes creates enforcement issues for employees in restaurants, bars, airport terminals, planes, and other smoke-free public places. E-cigarette companies are marketing their products to be used in all the places where smoking is banned, including bars, restaurants, hotels, offices, and airplanes, which promotes unregulated use.

Although the AHA supports the inclusion of e-cigarettes in new smoke-free laws, the AHA only supports changing existing smoke-free laws to include e-cigarettes when it can be ensured there will be no amendments attached to the legislation that would weaken existing laws.

Preventing Youth Access

The AHA supports the inclusion of e-cigarettes in state and federal laws and regulations that prohibit the sale of e-cigarettes to minors.

There is concern among public health advocates that e-cigarettes could increase nicotine addiction and serve as a gateway for the use of tobacco products, particularly among youth. As discussed above, adolescents view e-cigarettes as safer than conventional cigarettes, more convenient to use, and more readily accessible.⁴⁵ Their attraction to these “high-tech” devices is fueled further by the marketing practices of the tobacco industry, which is manufacturing flavored e-cigarettes that are likely to be more appealing to a younger population. To reduce the availability of e-cigarettes among youth, 22 states have enacted e-cigarette youth access laws and 6 states have youth access laws for tobacco-derived or nicotine-containing products without explicitly using “e-cigarette” or similar terms in their law.¹¹¹ For instance, Arizona, California, New Jersey, and New Hampshire have now banned e-cigarette sales to minors. In its proposed rule on “Deeming Tobacco Products to be Subject to the Federal Food, Drug, and Cosmetic Act” the FDA proposed to ban the sales of e-

cigarettes to consumers under the age of 18, which is similar to the existing federal ban on the sale of cigarettes and smokeless tobacco products to minors under the Family Smoking Prevention and Tobacco Control Act. Given that e-cigarettes are actively sold via Websites across state lines,¹⁰ it is essential to develop a comprehensive federal law or regulation banning e-cigarette sales to minors because state laws are a temporary patchwork approach¹¹² and only the federal government can regulate interstate commerce.^{113–115}

Marketing and Advertising to Youth

The AHA supports the inclusion of e-cigarettes in laws that restrict the marketing and advertising of e-cigarettes to minors.

There is robust marketing and advertising of e-cigarettes on television and in magazines using celebrities as well as flavorings to make these products particularly attractive to children and adolescents.¹⁰ Many of these advertisements have themes that promote rebelliousness and glamorize e-cigarette use, which conveys the message to youth that e-cigarette use is fun, socially acceptable, and desirable. Youth exposure to e-cigarette advertising increased more than 250% from 2011 to 2013, with e-cigarette advertisements reaching >24 million youths during this period.⁴⁸ Such marketing practices are likely to recruit a new generation of nicotine addicts. The public health community is unified in developing regulation and passing legislation that restricts the marketing and access of e-cigarettes to minors, similar to existing laws restricting marketing and youth access to combustible products.

Taxing E-Cigarettes

The AHA supports taxing e-cigarettes at a rate high enough to discourage youth use, while retaining or increasing differentials with combustible products by increasing taxes on combustibles. Any revenue generated through taxation ideally should support tobacco cessation and prevention programs.

The diversity of products makes it difficult to develop a uniform tax policy for various devices and refills, and it also creates opportunities for avoidance. An ad valorem tax, one levied as a percentage of price, preferably at the retail level, could include all components of e-cigarettes and related devices. However, a tax that is too high would create a barrier to switching to e-cigarettes among low-income users of combustible tobacco. Growing evidence shows that e-cigarette users are more responsive to price than cigarette use, with 1 study estimating that a 10% increase in e-cigarette prices would reduce sales of reusable e-cigarettes by $\approx 19\%$ and sales of disposable e-cigarettes by $\approx 12\%$.¹¹⁶ Similarly, data from a survey with adult tobacco users show that their low prices relative to other tobacco products is a key reason for use among many current e-cigarette users (F. Chaloupka, written communication, June 6, 2014).¹¹⁶ The initial cost of a reusable e-cigarette is higher, although over the long-term, they are cheaper because the reusable devices can be used over and over again. Hence, although a tax on the initial product could be punitive, especially for the low-income users, it is critical that the tax be high enough to deter youth access, because it has been demonstrated repeatedly that youth are especially price sensitive.^{118,119} At the same time, increasing taxes on combustible tobacco products would prevent youth uptake,

encourage some adult users to quit or cut back, and likely increase interest in switching from combustible products to e-cigarettes.

FDA Regulation of E-Cigarettes

The AHA supports effective FDA regulation of e-cigarettes that addresses marketing, youth access, labeling, quality control over manufacturing, free sampling, and standards for contaminants. The regulation should allow for quality-controlled products for adults who want to transition from conventional cigarettes to e-cigarettes or to quit or reduce smoking. Bottles containing nicotine refill liquids can be toxic if swallowed, so cartridges and bottles should have proper warning labeling and child-proof packaging.¹²⁰ It is important that the relevant government agency monitor whether these devices are used for delivery of other drugs and medications. Companies should not be able to claim that e-cigarettes are a cessation aid unless they are approved by the FDA for that purpose.

The FDA has currently issued its proposed rule to give the agency oversight over e-cigarettes, addressing youth access, sampling, ingredient listing, manufacturing, and warning labels, but not addressing marketing and advertising or flavorings. Some products currently on the market are unreliable and poorly designed, and there is inadequate and inaccurate labeling of constituents.^{121,122} Several companies are moving their manufacturing processes from China to the United States to prepare for the standardization and quality control that will be required under FDA oversight.¹²³ Adverse event reports regarding e-cigarette use are being monitored in many countries across the globe. In the United States, the Center for Tobacco Products under the FDA is developing a tobacco-specific adverse event reporting system for e-cigarettes. Consumers or healthcare providers can report adverse events for any tobacco products through the Department of Health and Human Services' Safety Reporting Portal.¹²⁴ The FDA would regulate e-cigarettes for tobacco cessation under current rules via the Center for Drug Evaluation Research, and as is the case for all other approved cessation aides, this would require rigorous safety and efficacy studies. FDA oversight is critically important to ensure that e-cigarettes and similar products are not harmful to public health.

The entry of the major US cigarette manufacturers (Altria Group, Reynolds American, and Lorillard) into the marketplace raises a number of potential public health concerns. Rather than encouraging cessation, the tobacco industry could promote e-cigarettes as a way to circumvent clean indoor air policies, thereby promoting dual use to sell more conventional cigarettes. The industry could also steer e-cigarette users to combustible products and thereby increase rather than decrease nicotine and tobacco addiction.¹²⁵ E-cigarette manufacturers are spending millions of dollars and working with major lobbying firms to pass legislation or influence regulation to exempt e-cigarettes or carve out a special classification.¹²⁶

In the European Union, starting in 2016, advertisements for e-cigarettes will be banned in all 28 nations, the packaging must be childproof and have graphic warning labels, and the nicotine content will be limited to 20 mg/mL.¹²⁷ The new regulations are part of a larger regulatory package that will impose even stricter rules on combustible tobacco products. The European Parliament backed off of its original proposal, which would have treated e-

cigarettes as a medical or drug-delivery device, but allows member states to categorize them as a cessation aid if member states choose to do so.¹²⁷

E-Cigarettes and the Potential to Regulate Nicotine Content of Conventional Cigarettes—The public health benefit of e-cigarettes competing with conventional cigarettes in a free marketplace is uncertain. Some potential harms, such as toxicity of unregulated products and marketing to youth, could be mitigated by effective FDA regulation. Possibly in the context of free market competition and perhaps with improved e-cigarette products, smokers would find e-cigarettes sufficiently attractive to use them to quit smoking. On the other hand, the permissive availability of e-cigarettes could result in an increase in nicotine addiction without a reduction in overall use of conventional cigarettes. A broader public health strategy could be developed that would combine regulation for combustible products, including regulation of characteristics and pricing, with the regulation of e-cigarettes or other electronic nicotine devices that appeal to smokers.¹²⁸ In 1994, the idea of reducing the nicotine content of cigarettes to make cigarettes less addictive was proposed, but the strategy was not implemented.¹²⁹ In 2009, the FDA gained regulatory authority over tobacco, which includes the authority to reduce nicotine in cigarettes to make them less addictive, as long as the nicotine level is not reduced to zero. Such a nicotine reduction regulatory policy could mandate nicotine reduction in all manufactured tobacco products so that they would not sustain addiction. Research is ongoing on the safety and the effects of smoking behavior with cigarettes with reduced nicotine content.^{130,131} If a reduced nicotine content regulatory strategy becomes policy, cigarettes could become less addictive because of limited nicotine availability, and therefore, less attractive to the smoker. If at the same time, e-cigarettes are widely available, it could potentially help the cigarette smoker to transfer their nicotine addiction from tobacco to a cleaner form of nicotine delivery. This transition could be facilitated by differential taxation and could reduce the burden of cigarette-induced disease. Nevertheless, at present, it remains unclear whether society would be accepting of recreational nicotine addiction if associated with minimal health consequences. Modeling the health effects of reducing the nicotine content of cigarettes to nonaddictive levels, Tengs et al¹³² concluded that “Policy makers would be hard-pressed to identify another domestic public health intervention, short of historical sanitation efforts, that has offered this magnitude of benefit to the population.”

Cessation Counseling

The AHA maintains that e-cigarette use should be part of tobacco screening questions incorporated into clinical visits and worksite/community health screenings that are tied to healthcare delivery. Clinicians should be educated about e-cigarettes and should be prepared to counsel their patients regarding comprehensive tobacco cessation strategies. There is not yet enough evidence for clinicians to counsel their patients who are using combustible tobacco products to use e-cigarettes as a primary cessation aid. The association will continue to monitor the evidence concerning e-cigarettes as cessation devices to determine whether they might be integrated into comprehensive cessation strategies. For patients with existing cardiovascular disease and stroke, or at risk of a cardiovascular disease

event, intensive cessation counseling should be offered as soon as possible. (See Table 2 for a summary of recommended clinical guidance.)

The efficacy of e-cigarettes as a primary smoking cessation aid has not been established as being better than other cessation modalities. Current evidence^{50,53,134} suggests at best a modest effect on cessation, likely equal to or slightly better than that of nicotine patches without behavioral support. If a patient has failed initial treatment, has been intolerant to or refused to use conventional smoking cessation medication, and wishes to use e-cigarettes to aid quitting, it is reasonable to support the attempt. However, subjects should be informed that although e-cigarette aerosol is likely to be much less toxic than cigarette smoking, the products are unregulated, may contain low levels of toxic chemicals, and have not been proven as cessation devices. Because there are as yet no long-term safety studies of e-cigarette use, it may be appropriate to advise the patient to consider setting a quit date for their e-cigarette use and not plan to use it indefinitely (unless needed to prevent relapse to cigarettes). It is also important to stress that patients should quit smoking cigarettes entirely as soon as possible, because continued cigarette smoking, even at reduced levels, continues to impose tobacco-induced health risks.

Employers will have to decide whether employees who use e-cigarettes exclusively will be considered tobacco users. Within the context of incentive design within healthcare plans associated with a worksite wellness programs, employers may charge tobacco users up to 50% more for their health insurance under the new Affordable Care Act regulations. There is no significant evidence that these tobacco surcharges increase quit rates, although 1 study showed that self-reported quit rates did increase more than the national average in Georgia State Health Benefit Plan employees.¹³⁵ With currently available methods, it is not possible to distinguish between a cigarette smoker and an e-cigarette user, because only the levels of cotinine are measured. Because cotinine is a metabolite of nicotine, it is likely to be present in the blood or urine of a user of e-cigarettes, combustible cigarettes, other tobacco products, and even nicotine patches. Hence, until newer methods are developed to distinguish between e-cigarettes and conventional cigarette use, employers would have to base their decisions primarily on self-report. Whether or not employers choose to penalize employees who are using e-cigarettes, employers should provide comprehensive cessation benefits to employees that include behavioral counseling and pharmacotherapy with a minimal copay or deductible for all users of tobacco products.

Insurance companies may also assess the 50% penalty in the individual market, although 10 states prohibit or restrict the ability of insurance companies to do that.^{136,137} Along with age, geographic location, and family size, tobacco use is 1 of 4 variables that insurers can take into account when selling plans on the individual market. The AHA is concerned that the tobacco surcharge will make it difficult for tobacco users to access the cessation services they need. At minimum, insurers in the individual marketplace, like employers, should provide comprehensive tobacco cessation benefits with minimal copays or deductibles for all e-cigarette and tobacco users.

Surveillance for E-cigarette Use and Health Impact

The AHA recognizes the need to improve and increase surveillance on e-cigarette use throughout the US and global population and establish a research agenda to elucidate the longitudinal public health impact of e-cigarette use.

There is a need to increase or maintain surveillance using high-quality longitudinal studies on the prevalence of e-cigarette use in adults, children, and adolescents; quit attempts; quit rates; e-cigarette rates versus smoking rates; dual use (with combustible tobacco or other tobacco products); and reinitiation of ex-smokers to e-cigarettes and then perhaps back to tobacco. Current surveillance should also include adequate reference to the emerging products entering the marketplace to ensure there is a thorough understanding of the true prevalence of use of these alternatives to combustible products. Surveillance should also capture how these devices are being used for delivery of other legal or illicit drugs. There must be further experimental research and surveillance on the short-, medium-, and long-term physiological effects of deep lung inhalation of not only the nicotine but also propylene glycol and glycerol, flavorings, and other ingredients. Experimental research and surveillance also needs to capture the long-term population health impact, effect on fetal development, and physiological and behavioral effects of these ingredients, as well as the health impact of secondhand and thirdhand exposure.

Defining E-Cigarettes in State Law

The AHA supports including e-cigarettes in the definition of tobacco products (or tobacco-derived products) and smoking, not by creating a separate definition for e-cigarettes, because a separate definition can create a risk of e-cigarettes being exempted from other tobacco control laws, including smoke-free laws. E-cigarettes defined as tobacco products could still be treated differently within taxation legislation and regulation.

Bringing e-cigarettes within a general definition of “tobacco products” in state or local law is also entirely consistent with their treatment under federal law. In *Sottera, Inc. (dba NJOY) v FDA* (627 F2d 891 [DC Cir 2010]), an e-cigarette manufacturer argued that its products could only be regulated by the FDA as tobacco products under the Family Smoking Prevention and Tobacco Control Act of 2009, not under the drug/device provisions of the Food, Drug, and Cosmetic Act.¹³⁸ The court agreed with the manufacturer, holding that e-cigarettes fit within the broad definition of *tobacco product* in the Tobacco Control Act (“any product made or derived from tobacco that is intended for human consumption”). The court further held that e-cigarettes could be regulated only under the Food, Drug, and Cosmetic Act if marketed with therapeutic claims. Thus, in *Sottera*, an e-cigarette manufacturer sought to be regulated by the FDA as a manufacturer of a “tobacco product,” and the court agreed that such regulation was within the FDA’s authority as a matter of federal law.^{138,139} These decisions were made although e-cigarettes do not actually contain tobacco, only nicotine derived from tobacco. The AHA agrees with the courts’ rulings in defining e-cigarettes as tobacco products in legislation and regulation and has worked with public health partners to develop a consensus definition of tobacco products that includes e-cigarettes (Table 3). This definition includes e-cigarettes even if they do not contain nicotine, that is, any electronic device that delivers nicotine or other substances. The inclusion of all e-cigarettes in the

definition facilitates implementation of laws and regulation. For example, when enforcing a clean indoor air policy, it would be impossible to determine whether someone who is “vaping” is using an e-cigarette that does or does not contain nicotine

Future Research Agenda

Because e-cigarettes are relatively new products, little is known about their use, their characteristics, or their long-term health effects on individual users and public health. Extensive research is required to address these questions. This will help in developing more robust policies to regulate e-cigarette use, marketing, and distribution. In view of the paucity of evidence, current guidelines must be regarded as provisional and should be revised in light of future research. However, e-cigarette research faces major challenges. E-cigarettes are not a well-defined entity but a collection of rapidly changing devices that deliver nicotine and contain a variety of additives that are also changing constantly. As a result, it is possible that research on specific e-cigarettes would become obsolete as product characteristics, design features, constituents, and additives change and new products appear on the market. Therefore, research will have to keep pace with the rapidly evolving market. Nonetheless, several invariant areas of future research could be identified, which are listed below.

Physicochemical Studies

Extensive work is required to develop a better understanding of the types of e-cigarettes currently in use and the ingredients they contain. To understand the nature of e-cigarette exposure, it is important to determine how heating time and duration of puffing alter exposure and the composition and characteristics of the vapor, as well as how each of these factors is affected by the design features of different devices. It will be important to evaluate how smoking e-cigarettes deposits nicotine and other chemicals in the environment and how these emissions and depositions affect secondhand and thirdhand exposures. Additional research is needed to evaluate the efficacy of vaping devices in delivering chemicals, drugs, and pharmaceuticals other than nicotine and to document manufacturing practices and quality control issues, so that the listed ingredients correspond to the actual composition of the device.

Perception

Profiles and perceptions of e-cigarette users have been documented in the literature; however, most of these data are derived from informal surveys from the Internet and other sources. New research is needed to determine the use and spread of e-cigarettes in different population subgroups and communities and to identify demographic factors that contribute to e-cigarette use in the general population. Additional research is also required to examine use trajectories, harm perception, and user expectations, as well as to determine how flavors affect perception and how future regulations might affect user profile and perception.

Use Pattern

Although extant data provide some indication of how e-cigarettes are currently being used, additional work is required to determine typical e-cigarette usage, with special emphasis on understanding brand/type preference and loyalty, frequency of use, brand switching, flavor

preference, and the effects of puff duration. These issues also relate to questions about optimal dosing, such as the optimal dose (or use) for cessation by product type and the dose and use patterns that sustain nicotine addiction or satisfy nicotine craving over time. It would be important to know whether and how these devices are being used to deliver other drugs and medication and whether their use is particularly widespread in vulnerable populations, such as youth, trendsetters, populations with low socioeconomic status, current smokers, ex-smokers, veterans, the mentally ill, those with substance use disorders, and the lesbian/gay/bisexual/transgender community.

Health Effects and Toxicity

Preclinical studies, preferably in animal models, are required to evaluate e-cigarette toxicity. Although animal models have obvious limitations, and their relevance to human exposures is often uncertain, these models could be useful in assessing the pharmacokinetic, pharmacodynamic, and toxicokinetic properties of e-cigarette exposures. Data from these studies will be useful in assessing acute and chronic toxicity, as well as the respiratory, carcinogenic, teratogenic, metabolic, immunological, and cardiovascular effects of e-cigarettes. The pathophysiological outcomes and biomarkers, identified in animal studies, should also be evaluated in controlled human exposure studies to develop validated concordance between animal and human data.

Data from in vitro and animal studies could inform the design of studies to evaluate the acute and chronic health effects of e-cigarettes. Acute effects could be evaluated in cross-sectional or cross-over studies examining the respiratory, metabolic, neurological, and cardiovascular effects, as well as the effects on insulin resistance, appetite, and weight loss. These data would be particularly informative and interesting if the health effects of e-cigarettes are compared directly with conventional cigarettes or other tobacco products. Such comparisons will help in identifying not only e-cigarette-specific health effects but also the effects common to e-cigarettes and other tobacco products. Because cross-sectional studies cannot establish directionality, progression, or causality, long-term longitudinal cohort studies are needed to assess how e-cigarette use affects the progression of subclinical disease. The results of well-powered, multicenter, prospective cohort studies with significant follow-up will provide important data for further refining policy recommendations.

Environmental Effects

Environmental research is needed to characterize e-cigarette emissions and to determine the chemical nature, size, and abundance of particulate matter generated in e-cigarette emission. In this research, it will be important to address the relative distribution of fine and ultrafine particles and to identify the chemical composition of these particles. Such studies are required to determine how changes in design features, additives, and constituents affect the direct toxicity of e-cigarette emissions. A particularly important issue that has direct bearing on regulation is the extent of secondhand and thirdhand exposure. Although e-cigarette emissions contain fewer chemicals and lower concentrations of toxicants than conventional cigarettes, the health effects of secondhand e-cigarette aerosol exposure are not known. Currently, most communities advocate the inclusion of e-cigarettes in smoking bans. This is justified because public use of e-cigarettes leads to involuntary exposure to a psychoactive

drug (nicotine) in bystanders. However, additional work is required to identify constituents of e-cigarette emissions, how these emissions are dispersed in the environment, and how the characteristics of the environment affect the dispersal and the health effects of such emissions.

Psychological Effects

Evaluation of the psychological effects of e-cigarettes is of utmost importance in understanding how the use of these devices supports or promotes nicotine addiction and whether they aid nicotine cessation or abstinence. Although the results of some studies suggest that as a cessation aid, e-cigarettes can be at least as effective as other NRTs, further work with larger cohorts is required to establish not only their efficacy as cessation aids but also how these devices affect nicotine addiction and withdrawal, as well as how they compare with other NRTs in user satisfaction and dependence. An important question is whether e-cigarette use merely facilitates abstinence from smoking conventional cigarettes or results in complete independence from nicotine addiction. In studying the use of these devices for cessation, it is important to determine whether counseling or behavioral support would enhance efficacy, and if so, what are the most effective instructions required for the proper use of these devices as a cessation aid? And should physicians and health providers counsel for or against e-cigarette use? Research findings addressing these questions are likely to have a major impact on our understanding of the nature of nicotine addiction and how it is supported by conventional cigarettes versus e-cigarettes. Again, prospective cohort studies with long-term follow-up will be most useful in assessing how e-cigarette use affects nicotine addiction.

Marketing and Communications

Marketing and communications research is needed to determine how e-cigarettes are being marketed and how information about them is being communicated to their target audience. Research is needed to identify how specific marketing techniques are used to target specific groups, which specific groups are being targeted, and what effects labeling, product placement, advertisements, free sample distribution, location in stores, and celebrity endorsement have on e-cigarette sales, preference, and use. Additional research is needed to identify effective communication techniques for conveying health information, potential hazard or benefit, and regulatory information. By establishing a partnership with consumers, it may be possible to identify consumer perceptions and expectations and to identify cultural, social, and economic factors that impact e-cigarette use.

Surveillance

Surveillance of e-cigarette use is just beginning at the national level in the United States and is generally lacking at the state and local level. At the national level, several surveys have been collecting information, including the National Youth Tobacco Survey in 2011 and 2012 (http://www.cdc.gov/tobacco/data_statistics/surveys/NYTS/), the National Health and Nutrition Examination Survey beginning in 2013 (http://www.cdc.gov/nchs/data/nhanes/nhanes_13_14/SMQ_ACASI_H.pdf), and the National Health Interview Survey beginning in 2014 (ftp://ftp.cdc.gov/pub/Health_Statistics/NCHS/Survey_Questionnaires/NHIS/2014/english/qadult.pdf). The Behavioral Risk Factor Surveillance System, a major source of

information regarding health behaviors at the state level, did not collect information about use of e-cigarettes as of 2013 (http://www.cdc.gov/brfss/questionnaires/pdf-ques/2013%20BRFSS_English.pdf).

The questions included in these surveys differ somewhat, primarily in the breadth of information collected. E-cigarette questions in the surveys above should use a similar format so the data can be pooled. Efforts to understand the public health impact of e-cigarettes require improved monitoring of awareness of the availability of e-cigarettes, beliefs about their health effects, and attitudes and behaviors regarding their use. Additional information is needed across the life span, especially in vulnerable groups, including children, and at the appropriate level to guide policy development, implementation, and evaluation; for these purposes, local and state-level data will be particularly important.

Postmarket surveillance is essential to understand and evaluate the public health impact of e-cigarettes. Such surveillance could include monitoring sales data, following the development and changes in the role of big tobacco companies and small entrepreneurs. Continuous pharmacovigilance is required to assess the safety and efficacy of these devices, changes in sales and marketing strategies, design features, and constituents. Such activities will be significantly facilitated by future regulation, which could define parameters for evaluating safety and regulatory compliance.

Economic Studies

Future research in economic issues relating to e-cigarettes is needed to evaluate the effect of taxation on e-cigarette sales and to assess the impact of e-cigarettes on healthcare costs and insurance premiums. Evaluation of the effect of taxation would be particularly important because this could have a significant impact on e-cigarette use across different populations. This type of research can be accomplished by both empirical research and observational studies, which will take longer and will require continuous analysis of sales data and purchasing behavior. Modeling work can be performed more quickly to predict what might happen with different approaches to taxation. Research in this area could be extended to include the cost of different devices and the contribution of e-cigarette sales to local and federal economies.

Legal and Regulatory Issues

Research is required to monitor and assess the effect of regulation on use, safety, and quality control and to determine the impact of legislation and regulation on industry and user responses.

Conclusions

E-cigarettes represent a major change in the tobacco control landscape. This policy guidance is developed from the current international evidence base and tobacco control environment in the United States. The AHA will continue to monitor the impact of these new technologies on population health, cardiovascular disease, and stroke and will give special attention to the effect on youth and adolescents. The association's policy position and

clinical guidance will evolve over time with the rapidly emerging research and evidence base for this field.

Appendix

Table 3 –

Definitions*

“Tobacco product” means:

- a. (a) Any product containing, made, or derived from tobacco or containing nicotine, whether synthetically produced or derived from other sources that is intended for human consumption (and not marketed for cessation), whether smoked, heated, chewed, absorbed, dissolved, inhaled, snorted, sniffed, or ingested by any other means, including, but not limited to cigarettes, cigars, little cigars, chewing tobacco, pipe tobacco, snuff[†]; and
- b. (b) Any electronic device that delivers nicotine or other substances to the person inhaling from the device, including, but not limited to an electronic cigarette, cigar, pipe, or hookah.
- c. (c) Notwithstanding any provision of subsections (a) and (b) to the contrary, “tobacco product” includes any component, part, or accessory of a tobacco product, whether or not sold separately. “Tobacco product” does not include any product that has been approved by the United States Food and Drug Administration for sale as a tobacco cessation product or for other therapeutic purposes where such product is marketed and sold solely for such an approved purpose.

It is important to note that this definition would include e-cigarettes, even if they do not contain nicotine. Thus, subsection (b) refers to “any electronic device that **delivers nicotine or other substances**” to cover devices (and components) regardless of whether they actually have nicotine or are being used to deliver nicotine. It was also recognized that there are alternative phrases that could be used to similarly expand coverage to non-nicotine products. For instance, the definition could refer to devices that “can be used to deliver nicotine.”

“Simulate Smoking” Language

It is not desirable to include language describing e-cigarettes as devices that are, or can be, used to “simulate smoking.” The vagueness of this phrase may give certain companies the opportunity to argue that their particular products are not covered since users are “vaping” instead of “smoking.” Given the wide variety of e-cigarette designs emerging in the exploding marketplace for these products, there is some potential for companies to argue that their particular design looks nothing like a cigarette and that its use cannot be said to “simulate smoking.” Because the phrase could have a limiting effect on the products covered, and does not appear to be needed to effectively regulate e-cigarettes, it would be best to avoid including it.

Separate Definition of “E-Cigarette”

Generally speaking, use of this “tobacco product” definition or similar language would obviate the need to include a definition of “e-cigarette” separate and distinct from the definition of “tobacco product.” However, in some states it may not be possible to include the full description of e-cigarettes in the tobacco product definition. Also, if special circumstances arise in a state that suggest the desirability of both including e-cigarettes as “tobacco products,” while also including a definition of e-cigarettes apart from the definition of “tobacco product,” a separate definition of e-cigarette could be adapted from subparts (b) and (c) of the consensus “tobacco product” definition:

E-cigarette[‡] means:

“Any electronic device that delivers nicotine or other substances to the person inhaling from the device, including but not limited to an electronic cigarette, cigar, pipe or hookah, including any component, part, or accessory of such a device, whether or not sold separately. E-cigarette shall not include any product that has been approved by the United States Food and Drug Administration for sale as a tobacco cessation product or for other therapeutic purposes where such product is marketed and sold solely for such an approved purpose.”

Finally, if a definition of “e-cigarettes” separate from the definition of “tobacco product” is desirable, then the definition of “tobacco product” will need to list “e-cigarettes” as one of the products to be considered “tobacco products.”

* These definitions were developed by an expert advisory group convened by the Campaign for Tobacco-Free Kids in April 2014. Participants were Chris Sherwin of the American Heart Association, Thomas Carr of the American Lung Association, Cathy Calloway of the American Cancer Society Cancer Action Network, and Nichole Veatch, Denny Henigan, and Ann Boonn of the Campaign for Tobacco-Free Kids.

[†] This list of products is subject to adjustment to conform to terms used in specific state or local laws.

[‡] Terms such as “electronic smoking device” or “electronic nicotine delivery systems” could be used interchangeably with “e-cigarettes.”

Appendix

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

Disclosures								
Writing Group Disclosures								
Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Aruni Bhatnagar	Director, Diabetes and Obesity Center, Smith and Lucille Gibson Professor, Division of Cardiovascular Medicine, University of Louisville, Co-Director, American Heart Association Tobacco Regulation and Addiction Center	None	None	None	None	None	None	None
Neal Benowitz	Professor of Medicine and Bioengineering & Therapeutic Sciences Chief, Division of Clinical Pharmacology University of California San Francisco	NIH grant: California Tobacco Related Disease Research Program ⁷ ; Flight Attendant Medic ⁸ Inst ⁷	None	None	2014: Plaintiff litigation against tobacco companies	None	Pfizer [*]	None
Chris Bullen	Director of the National Institute for Health Innovation and Associate Professor, School of Population Health, The University of Auckland, Auckland, New Zealand	In 2007, my group received funding from HealthNZ Ltd to conduct a small trial on Ruyan e-cigarettes; the product used in the trial was supplied by Ruyan Ltd.	Principal Investigator of the ASCEND e-cigarette efficacy trial, in which the e-cigarettes were provided by PGM International Ltd, a supplier of e-cigarettes (the trial was funded by the Health Research	None	None	None	Consultant on a USFDA/NIH cofunded TCORS grant on e-cigarettes	None

Disclosures								
Writing Group Disclosures								
Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
			Council of NZ)*					
Frank Chaloupka	Distinguished Professor, University of Illinois-Chicago	None	None	None	None	None	None	None
David Goff	Dean, Colorado School of Public Health	None	None	None	None	None	None	None
Timothy McAuley	Founder and Chief Executive Manager of Consulting for Health, Air, Nature, & a Greener Environment, LLC (CHANGE)	None	None	None	None	None	None	None
Mariann R. Piano	Professor of Nursing and Interim Head of the Department of Biobehavioral Health Science at the University of Illinois at Chicago College of Nursing	None	None	None	None	None	None	None
Rose Marie Robertson	American Heart Association Co-Director, American Heart Association Tobacco Regulation and Addiction Center	None	None	None	None	None	None	None
Kurt M. Ribisl	Professor, Health Behavior, University of North Carolina	None	None	None	None	None	None	None
Laurie P. Whitsel	Director of Policy Research, American Heart Association	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or

share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be “modest” if it is less than “significant” under the preceding definition.

* Modest.

† Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/ Honoraria	Expert Witness	Ownership Interest	Consultant/ Advisory Board	Other
Maciej Goniewicz	Roswell Park Cancer Institute	Pfizer-Global Research Awards for Nicotine Dependence (GRAND) 2011 [†]	None	None	None	None	None	None
Steve A. Schroeder	UCSF	Robert Wood Johnson Foundation [†]	American Legacy Foundation [†]	None	None	None	None	None
Kenneth Warner	University of Michigan	Robert Wood Johnson Foundation (finishing grant on the tobacco endgame) [*] ; Robert Wood Johnson Foundation (finishing grant on Tobacco Regulation Economics that relates to FDA's economic analysis of its graphic warning proposal) [*]	None	None	None	None	None	None
Rachel Widome	University of Minnesota	None	None	None	None	None	Association for Non-Smokers Minnesota [*]	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be “significant” if (a) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be “modest” if it is less than “significant” under the preceding definition.

* Modest.

† Significant.

References

1. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General, 2014. Rockville, MD: US Department of Health and Human Services; 1 2014.
2. Cummins SE, Zhu SH, Tedeschi GJ, Gamst AC, Myers MG. Use of e-cigarettes by individuals with mental health conditions. *Tob Control*. 2014;23(suppl 3):iii48–iii53. [PubMed: 24824516]

3. McClave AK, Whitney N, Thorne SL, Mariolis P, Dube SR, Engstrom M. Adult tobacco survey - 19 states, 2003–2007. *MMWR Surveill Summ.* 2010;59:1–75.
4. Gilbert H, inventor. Smokeless non-tobacco cigarette. US patent 3200819 A. 8 17, 1965.
5. Foulds J, Veldheer S, Berg A. Electronic cigarettes (e-cigs): views of aficionados and clinical/public health perspectives. *Int J Clin Pract.* 2011;65:1037–1042. [PubMed: 21801287]
6. Bell K, Keane H. Nicotine control: e-cigarettes, smoking and addiction. *Int J Drug Policy.* 2012;23:242–247. [PubMed: 22365155]
7. Ruyan asserts patent rights to e-cigarette in key China court ruling. Minneapolis, MN: Ruyan America: 2 23, 2009.
8. Troutman Sanders Tobacco Practice. Ruyan patent litigation as reason to consider patent protection. *Tobacco Law Blog.* 2014 <http://www.tobaccolawblog.com/2012/07/ruyan-patent-litigation-as-reason-to-consider-patent-protection/>. Accessed July 22, 2014.
9. Zhu SH, Sun JY, Bonnevie E, Cummins SE, Gamst A, Yin L, Lee M. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. *Tob Control.* 2014;23(suppl 3):iii3–iii9. [PubMed: 24935895]
10. Grana RA, Ling PM. “Smoking revolution”: a content analysis of electronic cigarette retail websites. *Am J Prev Med.* 2014;46:395–403. [PubMed: 24650842]
11. Hsu R, Myers AE, Ribisl KM, Marteau TM. An observational study of retail availability and in-store marketing of e-cigarettes in London: potential to undermine recent tobacco control gains? *BMJ Open.* 2013;3:e004085.
12. Rose SW, Barker DC, D’Angelo H, Khan T, Huang J, Chaloupka FJ, Ribisl KM. The availability of electronic cigarettes in US retail outlets, 2012: results of two national studies. *Tob Control.* 2014;23(suppl 3):iii10–iii16. [PubMed: 24935892]
13. Hadwiger ME, Trehy ML, Ye W, Moore T, Allgire J, Westenberger B. Identification of aminotadalafil and rimonabant in electronic cigarette products using high pressure liquid chromatography with diode array and tandem mass spectrometric detection. *J Chromatogr A.* 2010;1217:7547–7555. [PubMed: 20980012]
14. Herzog B, Gerberi J, Scott A. Equity research: Vapor--Revolutionizing the tobacco industry. San Francisco, CA: Wells Fargo Securities, LLC, Equity Research Department; 5 19, 2014.
15. McAuley TR, Hopke PK, Zhao J, Babaian S. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. *Inhal Toxicol.* 2012;24:850–857. [PubMed: 23033998]
16. Farsalinos KE, Romagna G, Alliffranchini E, Ripamonti E, Bocchietto E, Todeschi S, Tsiapras D, Kyrzopoulos S, Voudris V. Comparison of the cytotoxic potential of cigarette smoke and electronic cigarette vapour extract on cultured myocardial cells. *Int J Environ Res Public Health.* 2013;10:5146–5162. [PubMed: 24135821]
17. Czogala J, Goniewicz ML, Fidelus B, Zielinska-Danch W, Travers MJ, Sobczak A. Secondhand exposure to vapors from electronic cigarettes. *Nicotine Tob Res.* 2014;16:655–662. [PubMed: 24336346]
18. Ko mider L, Knysak J, Goniewicz ML, Sobczak A. Electronic cigarette: a safe substitute for tobacco cigarette or a new threat [in Polish]? *Przegl Lek.* 2012;69:1084–1089. [PubMed: 23421096]
19. Caponnetto P, Russo C, Bruno CM, Alamo A, Amaradio MD, Polosa R. Electronic cigarette: a possible substitute for cigarette dependence. *Monaldi Arch Chest Dis.* 2013;79:12–19. [PubMed: 23741941]
20. Abrams DB. Promise and peril of e-cigarettes: can disruptive technology make cigarettes obsolete? *JAMA.* 2014;311:135–136. [PubMed: 24399548]
21. Bertholon JF, Becquemin MH, Annesi-Maesano I, Dautzenberg B. Electronic cigarettes: a short review. *Respiration.* 2013;86:433–438. [PubMed: 24080743]
22. Brown CJ, Cheng JM. Electronic cigarettes: product characterisation and design considerations. *Tob Control.* 2014;23(suppl 2):ii4–ii10. [PubMed: 24732162]
23. Grana R, Benowitz N, Glantz SA. Background paper on e-cigarettes (electronic nicotine delivery systems). San Francisco, CA: Center for Tobacco Control Research and Education; 2013.
24. Adkison SE, O’Connor RJ, Bansal-Travers M, Hyland A, Borland R, Yong HH, Cummings KM, McNeill A, Thrasher JF, Hammond D, Fong GT. Electronic nicotine delivery systems:

- international tobacco control four-country survey. *Am J Prev Med.* 2013;44:207–215. [PubMed: 23415116]
25. Dockrell M, Morrison R, Bauld L, McNeill A. E-cigarettes: prevalence and attitudes in Great Britain. *Nicotine Tob Res.* 2013;15:1737–1744. [PubMed: 23703732]
 26. Pearson JL, Richardson A, Niaura RS, Vallone DM, Abrams DB. E-cigarette awareness, use, and harm perceptions in US adults. *Am J Public Health.* 2012;102:1758–1766. [PubMed: 22813087]
 27. Pepper JK, Reiter PL, McRee AL, Cameron LD, Gilkey MB, Brewer NT. Adolescent males' awareness of and willingness to try electronic cigarettes. *J Adolesc Health.* 2013;52:144–150. [PubMed: 23332477]
 28. Etter JF. Electronic cigarettes: a survey of users. *BMC Public Health.* 2010;10:231. [PubMed: 20441579]
 29. Pepper JK, Brewer NT. Electronic nicotine delivery system (electronic cigarette) awareness, use, reactions and beliefs: a systematic review. *Tob Control.* 11 20, 2013. doi:10.1136/tobaccocontrol-2013-051122. <http://tobaccocontrol.bmj.com/content/early/2013/11/20/tobaccocontrol-2013-051122>. Accessed July 22, 2014.
 30. Kralikova E, Kubatova S, Trunekova K, Kmetova A, Hajek P. The electronic cigarette: what proportion of smokers have tried it and how many use it regularly? *Addiction.* 2012;107:1528–1529.
 31. King BA, Alam S, Promoff G, Arrazola R, Dube SR. Awareness and ever-use of electronic cigarettes among U.S. Adults, 2010–2011. *Nicotine Tob Res.* 2013;15:1623–1627. [PubMed: 23449421]
 32. Choi K, Forster J. Characteristics associated with awareness, perceptions, and use of electronic nicotine delivery systems among young US midwestern adults. *Am J Public Health.* 2013;103:556–561. [PubMed: 23327246]
 33. Regan AK, Promoff G, Dube SR, Arrazola R. Electronic nicotine delivery systems: adult use and awareness of the “e-cigarette” in the USA. *Tob Control.* 2013;22:19–23. [PubMed: 22034071]
 34. European Commission TNS Opinion & Social. Attitudes of Europeans towards tobacco. Special Eurobarometer 385 5 2012.
 35. Zhu SH, Gamst A, Lee M, Cummins S, Yin L, Zoref L. The use and perception of electronic cigarettes and snus among the U.S. population. *PLoS One.* 2013;8:e79332. [PubMed: 24250756]
 36. Kralikova E, Novak J, West O, Kmetova A, Hajek P. Do e-cigarettes have the potential to compete with conventional cigarettes? A survey of conventional cigarette smokers' experiences with e-cigarettes. *Chest.* 2013;144:1609–1614. [PubMed: 23868661]
 37. Douptcheva N, Gmel G, Studer J, Deline S, Etter JF. Use of electronic cigarettes among young Swiss men. *J Epidemiol Commun Health.* 2013;67:1075–1076.
 38. Etter JF, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction.* 2011;106:2017–2028. [PubMed: 21592253]
 39. Dawkins L, Turner J, Roberts A, Soar K. “Vaping” profiles and preferences: an online survey of electronic cigarette users. *Addiction.* 2013;108:1115–1125. [PubMed: 23551515]
 40. Goniewicz ML, Zielinska-Danch W. Electronic cigarette use among teenagers and young adults in Poland. *Pediatrics.* 2012;130:e879–e885. [PubMed: 22987874]
 41. Sutfin EL, McCoy TP, Morrell HE, Hoepfner BB, Wolfson M. Electronic cigarette use by college students. *Drug Alcohol Depend.* 2013;131:214–221. [PubMed: 23746429]
 42. Grana RA, Popova L, Ling PM. A longitudinal analysis of electronic cigarette use and smoking cessation. *JAMA Intern Med.* 2014;174:812–813. [PubMed: 24664434]
 43. Dutra LM, Glantz SA. Electronic cigarettes and conventional cigarette use among US adolescents: a cross-sectional study. *JAMA Pediatr.* 3 6, 2014. doi:10.1001/jamapediatrics.2013.5488. <http://archpedi.jamanet-work.com/article.aspx?articleid=1840772>. Accessed July 21, 2014.
 44. Centers for Disease Control and Prevention (CDC). Notes from the field: electronic cigarette use among middle and high school students—United States, 2011–2012. *MMWR Morb Mortal Wkly Rep.* 2013;62:729–730. [PubMed: 24005229]
 45. Choi K, Fabian L, Mottey N, Corbett A, Forster J. Young adults' favorable perceptions of snus, dissolvable tobacco products, and electronic cigarettes: findings from a focus group study. *Am J Public Health.* 2012;102:2088–2093. [PubMed: 22813086]

46. Paek HJ, Kim S, Hove T, Huh JY. Reduced harm or another gateway to smoking? Source, message, and information characteristics of e-cigarette videos on YouTube. *J Health Commun.* 2014;19:545–560. [PubMed: 24117370]
47. The Public Health Cigarette Smoking Act of 1969, 15 USC §1331–1339 (1970).
48. Duke J, Lee YO, Kim AE, Watson KA, Arnold KY, Nonnemaker JM, Porter L. Exposure to electronic cigarette television advertisements among youth and young adults. *Pediatrics.* 2014;134:e29–e36. [PubMed: 24918224]
49. Ayers JW, Ribisl KM, Brownstein JS. Tracking the rise in popularity of electronic nicotine delivery systems (electronic cigarettes) using search query surveillance. *Am J Prev Med.* 2011;40:448–453. [PubMed: 21406279]
50. Harrell PT, Simmons VN, Correa JB, Padhya TA, Brandon TH. Electronic nicotine delivery systems (“e-cigarettes”): review of safety and smoking cessation efficacy. *Otolaryngology Head Neck Surg.* 6 4, 2014. doi:10.1177/0194599814536847. <http://oto.sagepub.com/content/early/2014/07/25/0194599814536847.long>. Accessed July 22, 2014.
51. Brown J, Beard E, Kotz D, Michie S, West R. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. *Addiction.* 5 20, 2014. doi:10.1111/add.12623. <http://onlinelibrary.wiley.com/doi/10.1111/add.12623/abstract>. Accessed July 22, 2014.
52. Vickerman KA, Carpenter KM, Altman T, Nash CM, Zbikowski SM. Use of electronic cigarettes among state tobacco cessation quitline callers. *Nicotine Tob Res.* 2013;15:1787–1791. [PubMed: 23658395]
53. Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, Walker N. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet.* 2013;382:1629–1637. [PubMed: 24029165]
54. Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. *Circulation.* 2014;129:1972–1986. [PubMed: 24821826]
55. Farsalinos K, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. *Ther Adv Drug Saf.* 2014;5:67–86. [PubMed: 25083263]
56. Grana RA, Ling PM, Benowitz N, Glantz S. Electronic cigarettes. *Circulation.* 2014;129:e490–e492. [PubMed: 24821830]
57. Orr MS. Electronic cigarettes in the USA: a summary of available toxicology data and suggestions for the future. *Tob Control.* 2014;23(suppl 2):ii18–ii22. [PubMed: 24732158]
58. Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PLoS One.* 2013;8:e57987. [PubMed: 23526962]
59. US Food and Drug Administration. Database of Select Committee on GRAS Substances (SCOGS) Reviews. Propylene glycol. 1973 <http://www.accessdata.fda.gov/scripts/fcn/fcnDetailNavigation.cfm?rpt=scogsListing&id=262>. Accessed June 9, 2014.
60. Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, Prokopowicz A, Jablonska-Czapla M, Rosik-Dulewska C, Havel C, Jacob P 3rd, Benowitz N. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control.* 2014;23:133–139. [PubMed: 23467656]
61. Palazzolo DL. Electronic cigarettes and vaping: a new challenge in clinical medicine and public health: a literature review. *Front Public Health.* 2013;1:56. [PubMed: 24350225]
62. Vaper Train. <http://www.vapertrain.com/page/hdics>. Accessed June 9, 2014.
63. Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine Tob Res.* 2013;15:267–270. [PubMed: 22311962]
64. Farsalinos KE, Spyrou A, Tsimopoulou K, Stefanopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Sci Rep.* 2014;4:4133. [PubMed: 24569565]
65. Centers for Disease Control and Prevention (US); National Center for Chronic Disease Prevention and Health Promotion (US); Office on Smoking and Health (US). *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General.* Atlanta, GA: Centers for Disease Control and Prevention; 2010.

66. Balakumar P, Kaur J. Is nicotine a key player or spectator in the induction and progression of cardiovascular disorders? *Pharmacol Res.* 2009;60:361–368. [PubMed: 19559087]
67. Arredondo J, Chernyavsky AI, Marubio LM, Beaudet AL, Jolkovsky DL, Pinkerton KE, Grando SA. Receptor-mediated tobacco toxicity: regulation of gene expression through alpha3beta2 nicotinic receptor in oral epithelial cells. *Am J Pathol.* 2005;166:597–613. [PubMed: 15681842]
68. Murray RP, Bailey WC, Daniels K, Bjornson WM, Kurnow K, Connett JE, Nides MA, Kiley JP; Lung Health Study Research Group. Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. *Chest.* 1996;109:438–445. [PubMed: 8620719]
69. Hubbard R, Lewis S, Smith C, Godfrey C, Smeeth L, Farrington P, Britton J. Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke, and death. *Tob Control.* 2005;14:416–421. [PubMed: 16319366]
70. Wennmalm A, Benthin G, Granström EF, Persson L, Petersson AS, Winell S. Relation between tobacco use and urinary excretion of thromboxane A2 and prostacyclin metabolites in young men. *Circulation.* 1991;83:1698–1704. [PubMed: 2022025]
71. Piano MR, Benowitz NL, Fitzgerald GA, Corbridge S, Heath J, Hahn E, Pechacek TF, Howard G; on behalf of American Heart Association Council on Cardiovascular Nursing. Impact of smokeless tobacco products on cardiovascular disease: implications for policy, prevention, and treatment: a policy statement from the American Heart Association. *Circulation.* 2010;122:1520–1544. [PubMed: 20837898]
72. Arefalk G, Hambraeus K, Lind L, Michaelsson K, Lindahl B, Sundstrom J. Discontinuation of smokeless tobacco and mortality risk after myocardial infarction. *Circulation.* 2014;130:325–332. [PubMed: 24958793]
73. Solarino B, Rosenbaum F, Riesselmann B, Buschmann CT, Tsokos M. Death due to ingestion of nicotine-containing solution: case report and review of the literature. *Forensic Sci Int* 2010;195:e19–e22.
74. Chatham-Stephens K, Law R, Taylor E, Melstrom P, Bunnell R, Wang B, Apelberg B, Schier JG. Notes from the field: calls to poison centers for exposures to electronic cigarettes—United States, September 2010–February 2014. *MMWR Morb Mortal Wkly Rep.* 2014;63:292–293. [PubMed: 24699766]
75. Vakkalanka JP, Hardison LS Jr, Holstege CP. Epidemiological trends in electronic cigarette exposures reported to U.S. poison centers. *Clin Toxicol (Phila).* 2014;52:542–548. [PubMed: 24792781]
76. Etter JF, Zather E, Svensson S. Analysis of refill liquids for electronic cigarettes. *Addiction.* 2013;108:1671–1679. [PubMed: 23701634]
77. Cameron JM, Howell DN, White JR, Andrenyak DM, Layton ME, Roll JM. Variable and potentially fatal amounts of nicotine in e-cigarette nicotine solutions. *Tob Control.* 2014;23:77–78. [PubMed: 23407110]
78. Harrington K E-cigarettes increase calls to poison control centers. In: Health News. [azfamily.com](http://www.azfamily.com/news/health/E-Cigarettes-increase-calls-to-Poison-Control-239534571.html). 1 10, 2014 <http://www.azfamily.com/news/health/E-Cigarettes-increase-calls-to-Poison-Control-239534571.html>. Accessed June 9, 2014.
79. E-cigarettes cause alarming increase in calls to poison control center. *The Lane Report.* 12 9, 2013.
80. Hecht SS. Biochemistry, biology, and carcinogenicity of tobacco-specific *N*-nitrosamines. *Chem Res Toxicol.* 1998;11:559–603. [PubMed: 9625726]
81. Kim HJ, Shin HS. Determination of tobacco-specific nitrosamines in replacement liquids of electronic cigarettes by liquid chromatography-tandem mass spectrometry. *J Chromatogr A.* 2013;1291:48–55. [PubMed: 23602640]
82. Jacob P 3rd, Hatsukami D, Severson H, Hall S, Yu L, Benowitz NL. Anabasine and anatabine as biomarkers for tobacco use during nicotine replacement therapy. *Cancer Epidemiol Biomarkers Prev.* 2002;11:1668–1673. [PubMed: 12496059]
83. Feng Z, Hu W, Hu Y, Tang MS. Acrolein is a major cigarette-related lung cancer agent: preferential binding at p53 mutational hotspots and inhibition of DNA repair. *Proc Natl Acad Sci U S A.* 2006;103:15404–15409. [PubMed: 17030796]

84. Ismahil MA, Hamid T, Haberzettl P, Gu Y, Chandrasekar B, Srivastava S, Bhatnagar A, Prabhu SD. Chronic oral exposure to the aldehyde pollutant acrolein induces dilated cardiomyopathy. *Am J Physiol Heart Circ Physiol*. 2011;301:H2050–2060. [PubMed: 21908791]
85. Srivastava S, Sithu SD, Vladykovskaya E, Haberzettl P, Hoetker DJ, Siddiqui MA, Conklin DJ, D'Souza SE, Bhatnagar A. Oral exposure to acrolein exacerbates atherosclerosis in apoE-null mice. *Atherosclerosis*. 2011;215:301–308. [PubMed: 21371710]
86. Goniewicz ML, Kuma T, Gawron M, Knysak J, Kosmider L. Nicotine levels in electronic cigarettes. *Nicotine Tob Res*. 2013;15:158–166. [PubMed: 22529223]
87. Kosmider L, Sobczak A, Fik M, Knysak J, Zaciera M, Kurek J, Goniewicz ML. Carbonyl compounds in electronic cigarette vapors: effects of nicotine solvent and battery output voltage. *Nicotine Tob Res*. 5 15, 2014 <http://ntr.oxfordjournals.org/content/early/2014/05/14/ntr.ntu078.long>. doi:10.1093/ntr/ntu078. Accessed July 22, 2014.
88. Robertson OH, Loosli CG, Puck TT, Wise H, Lemon HM, Lester W Jr. Tests for the chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapor inhalation and oral administration. *J Pharmacol Exp Ther*. 1947;91:52–76. [PubMed: 20265820]
89. Werley MS, McDonald P, Lilly P, Kirkpatrick D, Wallery J, Byron P, Venitz J. Non-clinical safety and pharmacokinetic evaluations of propylene glycol aerosol in Sprague-Dawley rats and beagle dogs. *Toxicology*. 2011;287:76–90. [PubMed: 21683116]
90. Wieslander G, Norbäck D, Lindgren T. Experimental exposure to propylene glycol mist in aviation emergency training: acute ocular and respiratory effects. *Occup Environ Med*. 2001;58:649–655. [PubMed: 11555686]
91. Fuoco FC, Buonanno G, Stabile L, Vigo P. Influential parameters on particle concentration and size distribution in the mainstream of e-cigarettes. *Environ Pollut*. 2014;184:523–529. [PubMed: 24172659]
92. Ingebrethsen BJ, Cole SK, Alderman SL. Electronic cigarette aerosol particle size distribution measurements. *Inhal Toxicol*. 2012;24:976–984. [PubMed: 23216158]
93. Peters A. Particulate matter and heart disease: evidence from epidemiological studies. *Toxicol Appl Pharmacol*. 2005;207:477–482. [PubMed: 15990137]
94. Pope CA 3rd, Burnett RT, Krewski D, Jerrett M, Shi Y, Calle EE, Thun MJ. Cardiovascular mortality and exposure to airborne fine particulate matter and cigarette smoke: shape of the exposure-response relationship. *Circulation*. 2009;120:941–948. [PubMed: 19720932]
95. Bahl V, Lin S, Xu N, Davis B, Wang YH, Talbot P. Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. *Reprod Toxicol*. 2012;34:529–537. [PubMed: 22989551]
96. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Spyrou A, Voudris V. Impact of flavour variability on electronic cigarette use experience: an Internet survey. *Int J Environ Res Public Health*. 2013;10:7272–7282. [PubMed: 24351746]
97. Romagna G, Alliffranchini E, Bocchietto E, Todeschi S, Esposito M, Farsalinos KE. Cytotoxicity evaluation of electronic cigarette vapor extract on cultured mammalian fibroblasts (ClearStream-LIFE): comparison with tobacco cigarette smoke extract. *Inhal Toxicol*. 2013;25:354–361. [PubMed: 23742112]
98. Behar RZ, Davis B, Wang Y, Bahl V, Lin S, Talbot P. Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. *Toxicol In Vitro*. 2014;28:198–208. [PubMed: 24516877]
99. Caponnetto P, Polosa R, Audatore R, Minutolo G, Signorelli M, Maglia M, Alamo A, Palermo F, Aguglia E. Smoking cessation and reduction in schizophrenia (SCARIS) with e-cigarette: study protocol for a randomized control trial. *Trials*. 2014;15:88. [PubMed: 24655473]
100. Vardavas CI, Anagnostopoulos N, Kougias M, Evangelopoulou V, Connolly GN, Behrakis PK. Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest*. 2012;141:1400–1406. [PubMed: 22194587]
101. Flouris AD, Chorti MS, Poulianiti KP, Jamurtas AZ, Kostikas K, Tzatzarakis MN, Wallace Hayes A, Tsatsakis AM, Koutedakis Y. Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhal Toxicol*. 2013;25:91–101. [PubMed: 23363041]

102. Polosa R, Morjaria J, Caponnetto P, Caruso M, Strano S, Battaglia E, Russo C. Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal. *Int J Environ Res Public Health*. 2014;11:4965–4977. [PubMed: 24814944]
103. Monroy A, Hommel E, Smith ST, Raji M. Paroxysmal atrial fibrillation following electronic cigarette use in an elderly woman. *Clin Geriatr*. 2012;20:28–32.
104. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Atlanta, GA: Centers for Disease Control and Prevention; 2006.
105. Schripp T, Markewitz D, Uhde E, Salthammer T. Does e-cigarette consumption cause passive vaping? *Indoor Air*. 2013;23:25–31. [PubMed: 22672560]
106. Schober W, Szendrei K, Matzen W, Osiander-Fuchs H, Heitmann D, Schettgen T, Jörres RA, Fromme H. Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. *Int J Hyg Environ Health*. 2013.
107. Kleinstreuer C, Feng Y. Lung deposition analyses of inhaled toxic aerosols in conventional and less harmful cigarette smoke: a review. *Int J Environ Res Public Health*. 2013;10:4454–4485. [PubMed: 24065038]
108. Sunstein CR. Social norms and social roles. *Columbia Law Review*. 1996;96:903–968.
109. McAdams RH. Focal point theory of expressive law. *Virginia Law Review*. 2000;86:1649.
110. Dohnke B, Weiss-Gerlach E, Spies CD. Social influences on the motivation to quit smoking: main and moderating effects of social norms. *Addict Behav*. 2011;36:286–293. [PubMed: 21183283]
111. Gourdet CK, Chriqui JF, Chaloupka FJ. A baseline understanding of state laws governing e-cigarettes. *Tob Control*. 2014;23(suppl 3):iii37–iii40. [PubMed: 24935897]
112. Paradise J. Electronic cigarettes: smoke-free laws, sale restrictions, and the public health. *Am J Public Health*. 2014;104:e17–e18. [PubMed: 24825224]
113. Banthin C. Cheap smokes: state and federal responses to tobacco tax evasion over the Internet. *Health Matrix Cleveland*. 2004;14:325–356. [PubMed: 15503692]
114. Ribisl K, Kim AE, Williams RS. Sales and marketing of cigarettes on the Internet: emerging threats to tobacco control and promising policy solutions In: Bonnie RJ, ed. *Ending the Tobacco Problem: A Blueprint for the Nation*. Washington, DC: National Academies Press; 2007.
115. Ribisl KM, Williams RS, Kim AE. Internet sales of cigarettes to minors. *JAMA*. 2003;290:1356–1359. [PubMed: 12966128]
116. Huang J, Tauras J, Chaloupka FJ. The impact of price and tobacco control policies on the demand for electronic nicotine delivery systems. *Tob Control*. 2014;23(suppl 3):iii41–iii47. [PubMed: 24935898]
117. Deleted in proof.
118. Carpenter C, Cook PJ. Cigarette taxes and youth smoking: new evidence from national, state, and local Youth Risk Behavior Surveys. *J Health Econ*. 2008;27:287–299. [PubMed: 18242745]
119. Chaloupka FJ. Macro-social influences: the effects of prices and tobacco-control policies on the demand for tobacco products. *Nicotine Tob Res*. 1999;1(suppl 1):S105–S109. [PubMed: 11072413]
120. Henningfield JE, Zaatari GS. Electronic nicotine delivery systems: emerging science foundation for policy. *Tob Control*. 2010;19:89–90. [PubMed: 20378582]
121. Uryupin A, Peregudov AS, Kochetkov KA, Bulatnikova LN, Kiselev SS, Nekrasov YS. Qualitative and quantitative compositions of fluids for electronic cigarettes. *Pharm Chem J*. 2013;46:687–692.
122. Cheah NP, Chong NW, Tan J, Morsed FA, Yee SK. Electronic nicotine delivery systems: regulatory and safety challenges: Singapore perspective. *Tob Control*. 2014;23:119–125. [PubMed: 23204074]
123. Mincer J. Quality issues push e-cigarette production to U.S. from China. *Reuters*. 5 25, 2014.
124. Federal Adverse Event Task Force; US Department of Health and Human Services. Safety reporting portal. <https://www.safetyreporting.hhs.gov/fpsr/WorkflowLoginIO.aspx?metinstance=BC3499CC0C3C50E4589B85F7E4C43E22B3AD53C0>. Accessed January 27, 2014.

125. Cullen D, Keithly L, Kane K, Land T, Paskowsky M, Chen L, Hayes R, Li W. Smokeless tobacco products sold in Massachusetts from 2003 to 2012: trends and variations in brand availability, nicotine contents and design features. *Tob Control*. 1 13, 2014. doi:10.1136/tobaccocontrol-2013-051225. <http://tobaccocontrol.bmj.com/content/early/2014/01/13/tobaccocontrol-2013-051225.abstract>. Accessed May 21, 2014.
126. Palmer A, Raju M. E-cigarettes reignite tobacco wars. *Politico Pro*. 1 24, 2014.
127. European parliament set to regulate electronic cigarettes. *Cheap Cigarettes Web site*. 5 8, 2014 <http://10cigarettes.com/european-parliament-set-to-regulate-electronic-cigarettes/>. Accessed online May 9, 2014.
128. Benowitz NL. Emerging nicotine delivery products: implications for public health. *Ann Am Thorac Soc*. 2014;11:231–235. [PubMed: 24575992]
129. Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction: the implications for tobacco regulation. *N Engl J Med*. 1994;331:123–125. [PubMed: 7818638]
130. Hatsukami DK, Kotlyar M, Hertsgaard LA, Zhang Y, Carmella SG, Jensen JA, Allen SS, Shields PG, Murphy SE, Stepanov I, Hecht SS. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. *Addiction*. 2010;105:343–355. [PubMed: 20078491]
131. Benowitz NL, Dains KM, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes. *Cancer Epidemiol Biomarkers Prev*. 2012;21:761–769. [PubMed: 22354905]
132. Tengs TO, Ahmad S, Savage JM, Moore R, Gage E. The AMA proposal to mandate nicotine reduction in cigarettes: a simulation of the population health impacts. *Prev Med*. 2005;40:170–180. [PubMed: 15533526]
133. Fiore MC JC, Baker TB. *Treating Tobacco Use and Dependence: 2008 Update Quick Reference Guide for Clinicians*. Rockville, MD: US Department of Health and Human Services; 2009.
134. Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, Polosa R. Efficiency and safety of an electronic cigarette (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLoS One*. 2013;8:e66317. [PubMed: 23826093]
135. Liber AC, Hockenberry JM, Gaydos LM, Lipscomb J. The potential and peril of health insurance tobacco surcharge programs: evidence from Georgia's State Employees' Health Benefit Plan. *Nicotine Tob Res*. 2014;16:689–696. [PubMed: 24376279]
136. Department of Health and Human Services. Patient Protection and Affordable Care Act: health insurance market rules: final rule. *Fed Regist*. 2013;78:13405–13442. [PubMed: 23476994]
137. Andrews M E-cigarette users may end up paying more for their health insurance. *Kaiser Health News*. 5 20, 2014.
138. *Sottera, Inc. vs. FDA*, 627 F2d 891 [DC Cir 2010] (2010).
139. *FDA v Brown and Williamson Tobacco Corp*, 529 US 120, 144 (2000).

Table 1.

Types of E-Cigarettes

Generation	Examples
<p>First generation</p> <p>First generation e-cigarettes were designed to look and feel like tobacco cigarettes. Although there is some variation in size, most resemble cigarettes and therefore have also been referred to as “cigalikes.” These battery-operated devices were initially composed of 3 pieces: a battery, atomizer, and cartridge. Now, the atomizer and cartridge have been replaced by a combined “cartomizer,” which screws into and connects with a battery, some of which are rechargeable. The disposable e-cigarettes are designed for 1-time use and are discarded after use. These cigalike devices are all available in various nicotine concentrations and with different flavorings.</p>	<p>Halo White Cloud Green Smoke Apollo Blu South Beach V2 Cigs Atlantic</p>
<p>Second generation</p> <p>These e-cigarette devices are larger and typically do not resemble a cigarette. These medium-battery (rechargeable)-style e-cigarettes are also referred to as “tank-styled” e-cigarettes. Sizes, shapes, and colors can resemble pens, small screwdrivers, or the tip of a hookah pipe. These larger e-cigarette devices have the basic e-cigarette components: the battery, the atomizer, and the cartridge. However, there are some key differences between these devices and the first-generation e-cigarette devices: second-generation e-cigarette devices have larger-capacity batteries (greater milliampere-hours) and therefore stay charged longer; have larger atomizers and electronic circuits that deliver greater energy (which enhances nicotine delivery to the user), and have large, separate cartridges (“tanks”) that the user can fill up using different purchased e-liquids and flavorings. Some also have a manual switch that allows modulation of both puff length and frequency.</p>	<p>eGo Riva Tornado KGo</p>
<p>Third generation</p> <p>These devices are similar to the second generation but are larger and allow for more personal and custom modifications; therefore, they are sometimes referred to as “personalized vapors” or aerosols. Similar to the second-generation devices, these devices come with a range of different cartridge and atomizer options (eg, cartomizer, clearomizer, tankomizer) and batteries (greater milliampere-hours coupled with a certain voltage [3.0–6.0 V]). Some e-cigarettes devices allow the user to adjust the resistance on the atomizer/cartomizer. A low-resistance cartomizer produces higher heating element temperatures, thus generating more heat and affecting the amount and quantity of the aerosol. Users of these devices can pair different atomizers (that allow different resistances) with high-capacity batteries to maximize both aerosol production and battery life.</p> <p>E-cigs could either be classified as a second- or third-generation e-cigarette device. Available in disposable and rechargeable forms. Designed to simulate a cigar in terms of size. Some e-cigs have an LED tip that is partially hidden behind some type of screen to mimic a real cigar’s ash.</p>	<p>Companies with personal vapors: Apollo Henly Vapor Zone Volcano</p> <p>E-cigar: Cuvana Marcello-rechargeable Vapor Zeus Royale premium</p>

E-cigs indicates electronic cigars; e-cigarettes, electronic cigarettes; LED, light-emitting diode.

Table 2.**Summary of Current Recommendations for Clinical Guidance**

E-cigarette use should be included in tobacco screening questions that are part of every health examination.

Clinicians should be educated about e-cigarettes and should be prepared to counsel their patients regarding comprehensive tobacco cessation strategies.

Patients should be separated into 3 treatment categories based on their tobacco/e-cigarette use status¹³³:

- 1** Tobacco product users who are willing to quit should receive intervention to help them quit
- 2** Tobacco product users unwilling to quit at the time should receive interventions to increase their motivation to quit
- 3** Those who recently quit using tobacco products should be provided relapse prevention treatment

There is not yet enough evidence for clinicians to counsel their patients who are using tobacco products to use e-cigarettes as a primary cessation aid.

If a patient has failed initial treatment, has been intolerant to or refuses to use conventional smoking cessation medication, and wishes to use e-cigarettes to aid quitting, it is reasonable to support the attempt. However, patients should be informed that although e-cigarette aerosol is likely to be much less toxic than cigarette smoking, the products are unregulated, may contain low levels of toxic chemicals, and have not been proven to be effective as cessation devices.

In the absence of long-term safety studies of e-cigarette use, it may be appropriate to advise the patient to consider setting a quit date for their e-cigarette use and not to plan to use it indefinitely (unless needed to prevent relapse to cigarettes).

It is also important to stress that patients should quit smoking cigarettes entirely as soon as possible, because continued cigarette smoking, even at reduced levels, continues to impose tobacco-induced health risks.

For patients with existing CVD or stroke, or at risk of a CVD event, intensive cessation counseling and pharmacotherapy should be offered as soon as possible.

CVD indicates cardiovascular disease; e-cigarette, electronic cigarette.