



Electronic Cigarettes—A Narrative Review for Clinicians

Menfil A. Orellana-Barrios, MD, Drew Payne, DO, Zachary Mulkey, MD, Kenneth Nugent, MD

Department of Internal Medicine, Texas Tech University Health Sciences Center, Lubbock.

ABSTRACT

Electronic cigarettes (e-cigarettes) were introduced into the US market in 2007 and have quickly become a popular source of nicotine for many patients. They are designed to simulate smoking by heating a nicotine-containing solution producing an aerosol that the user inhales. The short- and long-term effects of e-cigarette use are still unclear, but their use is increasing. Some acute effects of e-cigarettes on heart rate, blood pressure, and airway resistance are reported. Although there are some reports of improved cessation in a subset of users, there are also studies reporting decreased cessation in dual users of regular and e-cigarettes. Additionally, there is no current regulation of these devices, and this allows virtually anyone with a form of online payment to obtain them. © 2015 Elsevier Inc. All rights reserved. • *The American Journal of Medicine* (2015) 128, 674-681

KEYWORDS: Electronic cigarettes; Nicotine; Toxicity; Use patterns

Electronic cigarettes (e-cigarettes) are the most common type of a category of products called electronic nicotine delivery systems. E-cigarettes are relatively new products designed to simulate smoking by heating a solution that typically includes nicotine, flavorings, and a delivery system like propylene glycol or glycerin, or both. Other examples of these devices include cigars, pipes, and hookah-like products.^{1,2}

The first commercialized e-cigarette product was invented in 2003 and officially entered the US marketplace in 2007.^{3,4} These products have a particular nomenclature related to their use, and clinicians should know these terms to have productive conversations with patients (**Table 1**).^{2,4,5}

COMPOSITION, MARKETING, SALES DATA, AND RESPONSE FROM THE TOBACCO INDUSTRY

Construction

Electronic cigarettes have four parts: the battery, the heating element, the vaporizing chamber, and the solution cartridge (**Figure**).

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Requests for reprints should be addressed to Menfil A. Orellana-Barrios, MD, Department of Internal Medicine, Tech University Health Sciences Center, 3601 4th Street, MS 9410, Lubbock, TX 79430-9410.

E-mail address: menfil@gmail.com or ma.orellana-barrios@ttuhsc.edu

The battery is the power supply that provides the electrical current to the heating element needed to reach temperatures high enough to aerosolize the solution. This is usually a cylindrically shaped lithium ion rechargeable battery. The size and shape of the battery contributes significantly to the overall size and convenience of the e-cigarette; smaller devices allow easier transportability but usually need more frequent recharging. The lithium ion batteries provide higher voltages (>3 volts), necessary for producing the aerosol in the desired amounts, than traditional batteries (1.5 volts). There have been reports of these batteries overheating and exploding after being charged inappropriately or during an attempt to “light” the cigarette with a flame by mistake.⁶

The heating element provides the necessary heat for aerosolization of the nicotine solution. Many e-cigarette models include a voltage potentiometer that allows the user to select the amount of aerosol produced and nicotine concentration. A chamber houses the heating element and holds the aerosol until the user is ready to draw or inhale.

The solution cartridge contains the flavored nicotine solution (see **Table 1**) for aerosolization. This liquid includes a vehicle solution (propylene glycol, low molecular propylene glycol, or vegetable glycerin), artificial flavorings, and variable concentrations of nicotine. This may be refillable by the user or exchanged for prefilled cartridges. The number of choices in the composition of

e-cigarette solutions is increasing, and there is significant variability between the labeled content and the actual content and concentrations.⁴

Styles

E-cigarettes are available in a number of models and styles. Many take the appearance of traditional cigarettes—a “filter” at the bottom with white tubing and a red or orange glow tip. The “filter” is usually the cartomizer exterior (cartomizer = fusion of the cartridge and atomizer) and the “tobacco” part is usually the battery exterior. Others do not mimic the look of cigarettes, because some customers want to easily demonstrate they are not truly smoking in a nonsmoking area. Some companies have created an identity through a distinctive design that promotes brand recognition, such as the Blu eCig electronic cigarettes (Lorillard, Walpole, MA). Companies are also introducing customizable devices that allow multiple looks by using exchangeable exteriors.

Operation

The type of battery—automatic or manual—has an important role in how the e-cigarette is used. With an automatic battery, the user simply draws on the device like a traditional cigarette. With a manual battery, a button must be pressed to

activate the device and produce heating. The automatic type behaves more like traditional cigarettes.

Many e-cigarette models include a voltage potentiometer that allows the user to select the amount of aerosol produced, thereby selecting the amount of nicotine to be inhaled.⁷ Other operational details depend on the e-cigarette’s intended use. There are disposable models intended for one-time use. Others are intended for multiple uses and must be refilled either manually or with prefilled cartridges, and regular cleaning is necessary.

Marketing and Sales

In April 2014, the US Food and Drug Administration (FDA) announced plans to nationally regulate e-cigarettes like tobacco products.⁸ This includes restricted sales to minors and restricted advertising. Currently, the FDA’s Center for Tobacco Products is establishing a public docket in conjunction with a public workshop to gather information to advance the proposed regulation.⁹ Submission of comments ends in April 2015. Although some e-cigarette companies have announced their support of these proposed regulations, others are

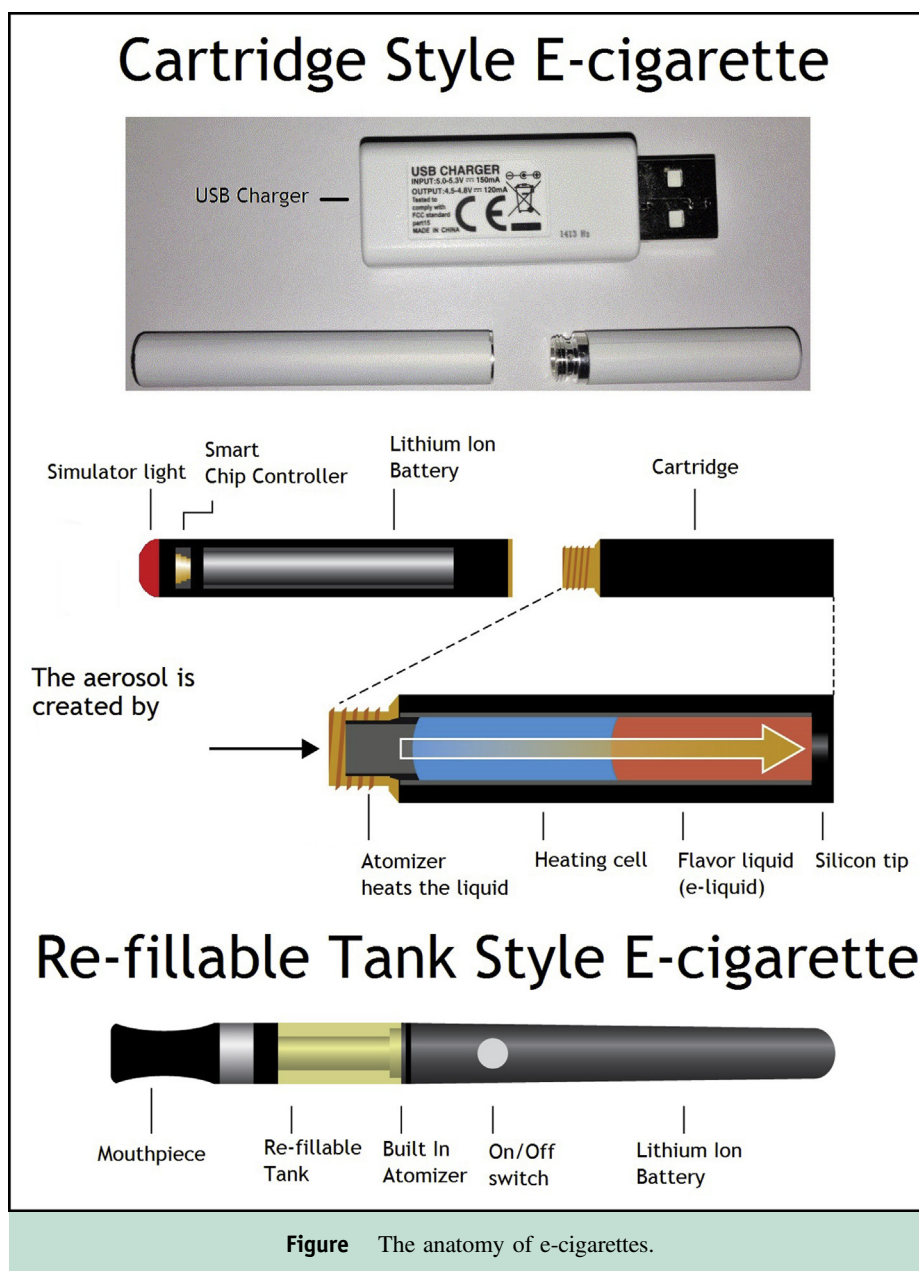
less enthusiastic. Until the regulations are finalized, the current state of the market is completely unregulated. The devices and the “e-juice” are available online to anyone with a means of online payment. Television and print ads are

CLINICAL SIGNIFICANCE

- E-cigarettes have become a popular source of nicotine.
- E-cigarettes have acute physiological effects, including increases in blood pressure, heart rate, and airway resistance.
- The long-term effects of e-cigarettes are unknown.
- There is insufficient evidence to recommend e-cigarettes for smoking cessation, although some reports of improved cessation exist. Dual use with regular cigarettes has been associated with decreased smoking cessation.
- E-cigarettes should not be viewed as “safe” as they can cause acute lung disease, atrial fibrillation, and nicotine poisoning.

Table 1 Electronic Cigarette Nomenclature

Name	Definition	Other Names
Electronic cigarette	The device designed to produce aerosol by heating the solution in the cartridge.	E-cig, smokeless cigarette, cig-a-like, vaporette, technofogger, personal vaporizer, vaping device, vapor pen, e-hookah.
Electronic cigarette use	The act of inhaling the heated aerosolized solution and subsequently exhaling is similar to smoking a regular cigarette.	Verbalized as “vaping.” An e-cigarette user may be described as a “vaper.” These terms are actually misnomers as the aerosol produced is technically not a vapor. The aerosol produced by e-cigarettes has a particulate phase, not just a gas phase like a vapor. ⁵
Electronic cigarette solution	The solution usually contains a mixture of propylene glycol or vegetable glycerin or both, with or without nicotine, and flavorings.	E-juice, e-liquid, juice, vapor juice, smoke juice
Hot cigarette Mods	A regular tobacco cigarette Modifications made to an e-cigarette used to produce higher amounts of aerosol	Cloud chaser, cloud chasing



becoming more common, some particularly aimed at the youth market.¹⁰ Sales of e-cigarettes have been estimated at approximately \$1.7 billion for 2013.¹¹

Big Tobacco

There are hundreds of e-cigarette companies in the US; most are small businesses that serve their local markets without a large online presence. Approximately 70% of the market belongs to 10 companies.¹² The big tobacco companies have entered the market by either buying some of the more successful small business startups or by creating their own e-cigarette brands. Lorillard (Walpole, MA: Newport brand) owns the Blu eCigs brand, and Phillip Morris (Miami, FL; Marlboro brand) recently bought out

the Green Smoke e-cigarette brand. Reynolds (Winston-Salem, NC; Camel brand) introduced its own e-cigarette brand called Vuse and had 55% market share in Colorado within 16 weeks. Philip-Morris USA/Altria Group market Mark 10 e-cigarettes.

USE PATTERNS IN THE PUBLIC: ADULTS, TEENAGERS, PREGNANCY

The use of electronic cigarettes by children is increasing in the US, but remains much lower than use of traditional tobacco products. Recent data note that e-cigarette use by both high school and junior high students has increased, and reportedly over a quarter of a million never-smoking youths had tried e-cigarettes by 2013.¹³⁻¹⁵ These data also show

that during the same period, use of traditional cigarettes has decreased in these two groups. It appears that children and young adults are trying e-cigarettes on an experimental basis without intending to replace traditional cigarettes or to start a pattern of regular usage. College students often use e-cigarettes as replacements for traditional cigarettes either as a “safer alternative” or for experimentation.¹⁶

Use by adults is also increasing, and 21% of adults surveyed reported trying e-cigarettes in 2012, up from 10% in 2010. Adults also report using e-cigarettes as cessation tools and safer alternatives to traditional cigarettes.^{17,18} There are currently no data on either prevalence or biologic effects of e-cigarette use during pregnancy. It is important that clinicians recognize that any nicotine exposure is deleterious to maternal and fetal health.¹⁹

REGULATION BY THE FDA OR OTHER NATIONAL/INTERNATIONAL ENTITIES

The FDA has issued a proposed rule that would extend the regulation of e-cigarettes as tobacco products by the Food, Drug, and Cosmetic Act.⁸ Currently, only e-cigarettes marketed for therapeutic purposes are regulated by the FDA Center for Drug Evaluation and Research. Regular cigarettes are regulated by the FDA Center for Tobacco Products.²⁰ The US will join other countries that have already initiated this process. In essence, the regulation of electronic cigarettes would mirror that of traditional tobacco products in terms of sales to minors and allowable marketing techniques. It does not include specific regulations on flavored or zero nicotine “e-juice.” States and individual municipalities will still be responsible for regulating the use of e-cigarettes in public places. Some countries, including Australia, Mexico, Brazil, Argentina, and Columbia, have completely banned e-cigarettes.

In February 2014, the European Parliament issued a Memorandum of the EU Tobacco Products Directive regulating e-cigarettes (including solution composition, advertising, and marketing strategies), recognizing their increasing use and market and stating that as they are nicotine-containing products, safety and quality regulations

are necessary. Products that do not contain nicotine will not be regulated by the Directive.²¹ Specific regulations, such as age limits, are to be set by individual members of the EU.

BIOLOGIC EFFECTS

Acute Physiological Effects

Table 2²²⁻³⁰ outlines the reported physiological effects of e-cigarette use.

Nicotine Levels

One important aspect of e-cigarette use is that these devices are designed to deliver nicotine via the lungs. There are substantial differences in the amounts delivered by e-cigarettes compared with regular cigarettes and by different e-cigarette brands. Studies with automated smoking machines show that e-cigarettes deliver less nicotine per puff than regular cigarettes. However, the smoking “technique” does affect the actual nicotine delivered, as inexperienced e-cigarette smokers achieve lower serum nicotine concentrations than experienced e-cigarette smokers who achieve systemic concentrations similar to regular cigarettes.³¹ In a study conducted with experienced e-cigarette users, the mean salivary cotinine (the principal metabolite of nicotine) levels were 322 ng/mL.³² Mean salivary cotinine levels for regular cigarette smokers were 113 ng/mL, and 2.4 ng/mL for nonsmokers in one report.³³

E-cigarettes have a liquid reservoir of concentrated nicotine, and unintentional exposures from the ingestion of this liquid have been reported. Also, intentional intoxication by injection and ingestion, suicide attempts, and completed suicides associated with these concentrated nicotine vials have been reported. Nicotine is rapidly absorbed in lungs, skin, and mucous membranes, and the lethal dose ranges from 10 to 60 mg. As some e-cigarette liquids contain nicotine at a concentration of around 100 mg/mL, this presents the potential for lethal toxicity.³⁴⁻³⁶ Additionally, instances of “no nicotine” solutions actually containing nicotine have been reported.³¹

Table 2 Reported Physiologic Effects of E-cigarette Use

Parameter	Effect	Source
Serum carbon monoxide levels	No definite effect with contradicting studies	22,23
Diastolic blood pressure	Significant increase	24
Systolic blood pressure	No significant increase	24
Ventricular systolic and diastolic function	No effect	24
Heart rate	Significant increase after 5 and 10 minutes of use	22,23
Blood counts	No change in WBCs, lymphocytes and granulocytes	25,26
Exhaled nitric oxide (FeNO)	Significant decrease shortly after use	27,28
Respiratory impedances (a marker of peripheral airway flow resistance)	Significant (18%) increase	28
Airway resistance	Significant increase, including nicotine free solutions	29,30

Exposure to Chemical Substances Other Than Nicotine

Many substances have been identified in e-cigarette solutions, including tobacco-specific nitrosamines, tobacco alkaloids, aldehydes, metals, volatile organic compounds, polycyclic aromatic hydrocarbons, flavors, solvent carriers, and drugs (tadalafil and rimonabant).³⁷ The reported metals in aerosols and cartridges of e-cigarettes include cadmium, nickel, lead, chromium, and arsenic.³⁸ One report indicated that levels of nickel were 100 times higher than in regular cigarettes.³⁹ Carbonyl compounds have also been reported present in e-cigarette aerosol.⁴⁰ The liquid composition of each brand of e-cigarette may differ, making it difficult to generalize about the potential toxic properties of these devices.

“Second-hand Vapor”

In contrast to regular cigarettes, which are in constant combustion when used, e-cigarettes release aerosols when the user exhales. Study of airborne particle production related to e-cigarette use is needed to determine any “second-hand” effects. It has been reported that consumption of e-cigarettes causes significant aerosol emissions and nicotine into indoor air.⁴¹⁻⁴³ Additionally, e-cigarettes chamber studies have proven that they are a source of “third-hand” exposure to nicotine from surfaces exposed to exhaled e-cigarette vapor.⁴⁴

ROLE IN SMOKING CESSATION

The published data on e-cigarettes for smoking reduction or cessation are conflicting. To date, smaller trials, not necessarily designed to measure smoking cessation, have not shown a benefit of e-cigarette use in cessation outcomes.⁴⁵⁻⁴⁷ Although manufacturers have promoted these devices for cessation since their introduction into the market, this has not been FDA approved, and no current applications have been submitted for approval of this indication.

Survey and observational data have reported conflicting results. One particularly large survey reported 81% complete smoking substitution with a median time of e-cigarette use of 10 months.⁴⁸ Another “real-world” survey reported higher abstinence at 12 months with e-cigarettes use than with other nicotine replacements and no aid.¹⁸ Recently, a longitudinal study of smokers and e-cigarette use reported that daily users of e-cigarettes were 6 times as likely as nonusers/riers to report quitting.⁴⁹

In contrast, a study of smoking cancer patients referred to a tobacco cessation program reported e-cigarette users were twice as likely to be smoking at follow-up as compared with nonusers, after adjusting for nicotine dependence, quit attempts, and cancer diagnosis. In this study, e-cigarette users were more nicotine dependent.⁵⁰ Also, a large Korean Web-based survey showed that current cigarette smokers were much more likely to use e-cigarettes than were nonsmokers.⁵¹ In the longitudinal study cited above,

intermittent e-cigarette use was negatively associated with the motivation to quit.⁴⁹ These studies suggest that e-cigarette use and particularly, dual use, could reduce the likelihood of quitting.

Two clinical trials have been completed,^{52,53} and 2 are ongoing [NCT01979796, NCT01785537]^{54,55} on the use of e-cigarettes specifically for smoking reduction or cessation. The first trial^{52,56} included 657 subjects and found that at 6 months the verified abstinence rates were 7.3%, 5.8%, and 4.1% with nicotine-containing e-cigarettes, nicotine patches, and placebo e-cigarettes, respectively. This study did not demonstrate any superiority of nicotine e-cigarettes compared with the other treatments. The ECLAT^{53,57} trial included 300 smokers who did not intend to quit. They were divided into 3 groups: 2 were offered different nicotine concentrations in e-cigarettes, compared with a third placebo group. The authors concluded that the use of e-cigarettes, with or without nicotine, decreased cigarette consumption and facilitated sustained tobacco abstinence without causing significant side effects.

Dual Use

Dual use of e-cigarettes and regular cigarettes has been reported as the main pattern of use, and there is some evidence that this might be associated with increased nicotine dependence.⁵⁰ Among middle school and high school students, dual use was found in 61%-81% of users.¹ In one large Internet survey, continued dual use was reported at 19%, with only 3.5% of participants using zero nicotine solutions.⁴⁸ It is important that the clinician identify this dual use pattern and the clinical implications of e-cigarettes being an additional (rather than substituting) source of nicotine.

E-CIGARETTE TOXICITY

Reported adverse events related to e-cigarettes are usually mild to moderate and transient. However, e-cigarette exposure calls to poison control centers are increasing; for example, a 2014 study including Texas poison control centers found 2, 6, 11, and 43 reports in 2009, 2010, 2011, and 2012, respectively.⁵⁸ The reported events include nausea, vomiting, mouth and airway irritation, chest pain, and palpitations.⁵⁹

Lung

Limited controlled studies are available on the safety of e-cigarettes or long-term health effects. There is little knowledge or regulation of the composition of each device or vaping liquid, and health officials do not know the effects on the lungs and heart or the risk for cancer. Nicotine, volatile organic compounds, heavy metals, and particle irritants are risks highlighted in recent studies.

Documented acute adverse effects on the lungs have been limited to case reports and existing knowledge of material contained within the e-liquid. Significant exposure to the

primary ingredient of the e-liquid, propylene glycol, while generally considered by the FDA to be safe, can cause irritation to the upper and lower respiratory track mucosa. A case of eosinophilic pneumonia 1 hour after smoking an e-cigarette has been reported.⁶⁰ This patient was treated with antibiotics and steroids and improved. There is also a reported case of lipoid pneumonia attributed to the glycerin-containing solution used in e-cigarettes. This patient's symptoms and chest radiograph returned to normal after quitting e-cigarette use.⁶¹ Another case report described the temporal association between sub-acute bronchiolitis and the use of e-cigarettes. Symptoms and pulmonary function tests returned to baseline after e-cigarette cessation without other treatment.⁶² Although uncommon, these cases point to the unpredictable and potentially serious side effects of e-cigarettes.

Cardiovascular

E-cigarette use can increase the heart rate and blood pressure and has the potential to cause cardiac events and arrhythmias in individuals with or at risk for cardiac disease.⁶³ However, studies using echocardiographic assessment of cardiac function did not show any effects after e-cigarette use.²⁴ There has been one case report of a temporal association between e-cigarette use and paroxysmal atrial fibrillation in a 70-year-old woman.⁶⁴ Most of the presumed cardiac effects are thought to be secondary to the nicotine delivered by e-cigarettes. Although smokeless tobacco-associated cardiac events have been studied in the past, it is difficult to extrapolate data to e-cigarettes, considering their different mechanism of nicotine delivery.⁶⁵ There are currently no published studies on e-cigarette use and thrombosis, platelet reactivity, atherosclerosis, or blood vessel function.

Cancer Risk

The long-term effect of e-cigarette use on cancer risk is unknown. However, e-cigarette users can be exposed to known carcinogens. One study compared the aerosol generated from 12 brands of e-cigarettes with regular cigarette smoke.⁶⁶ The e-cigarette aerosol contained lower levels of toxicants compared with cigarettes. Carcinogen levels were 9 to 450 times lower than those in conventional tobacco products. However, a more recent study utilizing the newer "tank-style" systems with higher voltage batteries reported that these e-cigarettes might expose users to equal or even greater levels of carcinogenic formaldehyde than in tobacco smoke.⁴⁰

The heating element in the e-cigarette causes the incidental generation of carbonyl compounds in e-cigarette smoke mist.^{40,67} The vaping liquid products (glycerol and propylene glycol) are oxidized into formaldehyde, acetaldehyde, acrolein, glyoxal, and methylglyoxal. A 2009 study commissioned by the FDA found known carcinogens diethylene glycol and nitrosamines in trace amounts.⁶⁸ Diethylene glycol is an organic compound used as a

solvent and is currently banned from food and drugs. Nitrosamine is a known carcinogen found in cosmetics, pesticides, and most rubber products.

STATEMENTS MADE BY NATIONAL MEDICAL SOCIETIES

The Tobacco Control Committee of the American Thoracic Society, in conjunction with the Forum of International Medical Societies, issued this statement in July 2014: "As a precaution, electronic nicotine delivery devices should be restricted or banned until more information about their safety is available." The American Thoracic Society does not endorse e-cigarettes as a smoking cessation aid, noting the lack of FDA approval.⁶⁹

The American Heart Association (AHA) has recently issued a Policy Statement recognizing the increase in e-cigarette use and the need to develop a clear policy on their use. The statement acknowledges that e-cigarette use has the potential to renormalize smoking behavior, sustain dual use, and initiate or maintain nicotine addiction. The statement also recognizes the potential of e-cigarettes for harm reduction if current smokers use them as substitutes for regular cigarettes. 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. As yet, the AHA finds the available evidence insufficient to promote e-cigarettes as a smoking cessation aid.⁷⁰

STATEMENTS MADE BY INTERNATIONAL MEDICAL SOCIETIES

The World Health Organization published an extensive review on the topic of e-cigarettes: "Background Paper on E-cigarettes (Electronic Nicotine Delivery Systems)" in 2013.³ The Spanish Society for Pulmonary Medicine and Thoracic Surgery has issued an official communication advocating for the regulation of e-cigarettes as a medicinal product, and stating that there is insufficient evidence to use e-cigarettes for smoking cessation.⁷¹

CONCLUSIONS

Current studies report increased use of e-cigarettes by teens and adults. Based on a few studies, e-cigarettes appear to have some immediate adverse health effects, but studies reporting long-term effects on pure e-cigarette users as well as dual users are needed. E-cigarette use as a tobacco cessation product is not currently FDA approved, and a recent FDA-proposed regulation signals a possible change in FDA position toward the e-cigarette industry. Regarding e-cigarette use as a smoking cessation aid, some survey data do show improved cessation, particularly with "intensive" e-cigarette use. However, dual use has been associated with failed smoking cessation in several studies. The health effects of "intensive" e-cigarette

use are unknown. As e-cigarette manufacturing changes, the newer and “hotter” products may expose patients to higher levels of known carcinogens. Physicians have a responsibility to understand these devices and to know about possible adverse effects. As e-cigarette use increases, patients and physicians will need to communicate effectively about this inhaled nicotine product. Useful Patient Education pages have been published in English and Spanish and may be used by physicians and smoking cessation programs.^{72,73}

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