

## REVIEW ARTICLE

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## The Health Effects of Electronic Cigarettes

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**E**LECTRONIC CIGARETTES (E-CIGARETTES), ALSO KNOWN AS ELECTRONIC nicotine-delivery systems, are devices that produce an aerosol by heating a liquid that contains a solvent (vegetable glycerin, propylene glycol, or a mixture of these), one or more flavorings, and nicotine, although the nicotine may be omitted. The evaporation of the liquid at the heating element is followed by rapid cooling to form an aerosol. This process is fundamentally different from the combustion of tobacco, and consequently the composition of the aerosol from e-cigarettes and the smoke from tobacco is quite different. E-cigarette aerosol is directly inhaled (or "vaped") by the user through a mouthpiece. Each device includes a battery, a reservoir that contains the liquid, and a vaporization chamber with heating element (Fig. 1). The design of the e-cigarette was originally based on the design of conventional cigarettes but has since evolved, with later-generation devices permitting users to refill a single device with different liquids and to customize the heating element.<sup>1</sup>

The inhalation of aerosol from a nicotine-containing e-cigarette leads to peak serum nicotine concentration within 5 minutes.<sup>2</sup> This rapidity of systemic delivery, combined with a method of use that is the same as that used for conventional cigarettes (i.e., oral inhalation), results in an experience for the user that is closer to cigarette smoking than the forms of nicotine-replacement therapy that have been approved by the Food and Drug Administration (FDA). In 2014, there were an estimated 466 brands and 7764 unique flavors of e-cigarette products<sup>3</sup>; this heterogeneity complicates research on potential health effects. The scientific, regulatory, and lay communities have been impassioned but divided in their responses to e-cigarettes,<sup>4</sup> with some advocating their use on the basis of "harm reduction" as compared with tobacco smoking, and others championing the so-called precautionary principle, which is based on a philosophy that avoids adoption of a new product when the long-term effects of that product are unknown.<sup>5</sup>

## PREVALENCE AND PATTERNS OF USE

In 2010, a total of 1.8% of U.S. adults reported having used an e-cigarette at some time, a rate that rose to 13.0% by 2013; reports of "current use" increased from 0.3% to 6.8% during this period.<sup>6</sup> Although tobacco smokers were among those most likely to be current users of e-cigarettes, a third of current e-cigarette users had never smoked tobacco or were former tobacco smokers.<sup>6</sup> A survey of 4444 college students from eight colleges in North Carolina showed that e-cigarette use was not motivated by the desire to stop smoking cigarettes.<sup>7</sup> A U.S. population survey indicated that adults with mental health conditions such as anxiety disorders and depression were more likely to use e-cigarettes than adults without those conditions.<sup>8</sup>

Of particular concern regarding public health has been the increasing experimen-

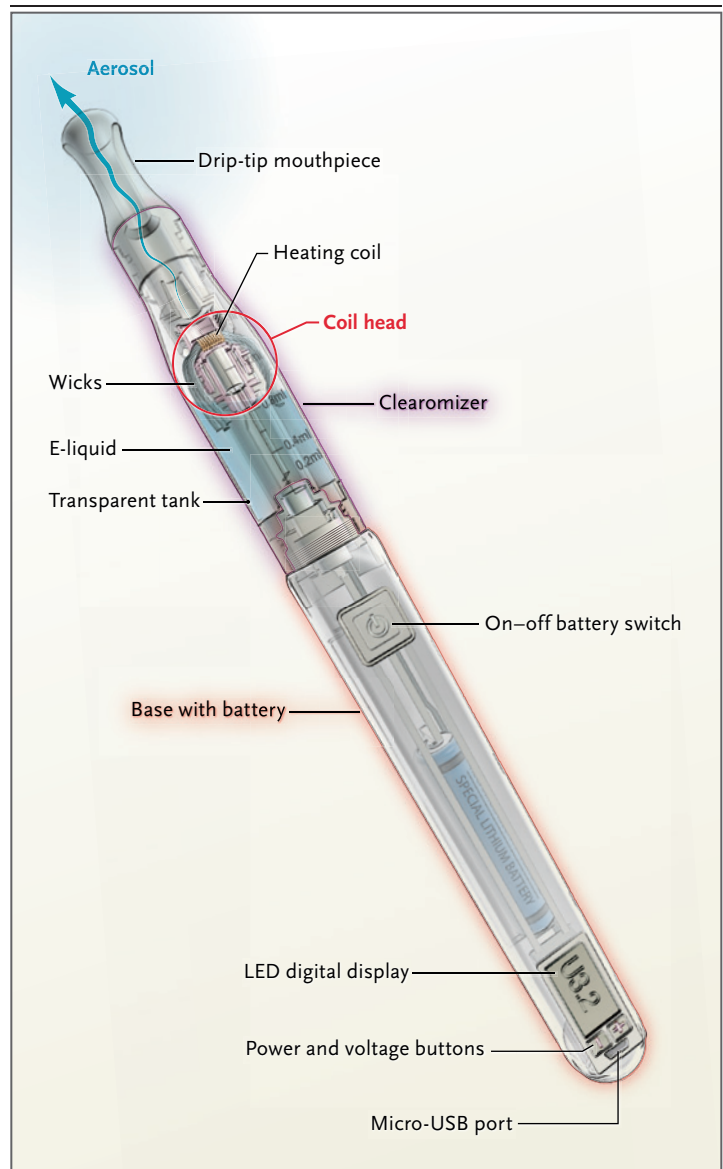
tation with and use of e-cigarettes among persons younger than 18 years of age. In 2013, an estimated 263,000 middle-school and high-school students who had never smoked a conventional cigarette reported having used e-cigarettes.<sup>9</sup> In this age group, e-cigarette use continues to increase, with 16% of high-school students in 2015 reporting any use within the preceding 30 days, whereas conventional cigarette smoking declined through 2014 and then remained unchanged in 2015.<sup>10</sup> Recent data suggest that e-cigarette use by youths of high-school age may be associated with an increased risk of subsequent tobacco smoking.<sup>11</sup> A limitation of these reports is the variability in the definitions of “current” use of e-cigarettes and the potential misclassification of regular use and infrequent experimentation.

The reasons for the increasing use of e-cigarettes by minors (persons between 12 and 17 years of age) may include robust marketing and advertising campaigns that showcase celebrities, popular activities, evocative images, and appealing flavors, such as cotton candy. E-cigarettes are marketed on the Internet and social media outlets<sup>12</sup> and are increasingly advertised on television and radio and in shopping malls and print media. In the United States, the exposure of minors to television advertisements for e-cigarettes increased 256% between 2011 and 2013, with as many as 24 million minors exposed to these advertisements in 2013.<sup>13</sup> National survey data suggest an association between exposure to e-cigarette advertising and the use of these products among students in middle school and high school.<sup>14</sup>

Although the sale of e-cigarettes is prohibited in some countries, it is legal in most, including the United States, where the FDA recently finalized rules for the regulation of e-cigarettes as a tobacco product. The U.S. market for e-cigarettes is now estimated to be worth \$1.5 billion, a number that is projected to grow by 24.2% per year through 2018.<sup>15</sup> Global sales are predicted to reach \$10 billion by 2017.<sup>16</sup>

#### E-CIGARETTES AS A SMOKING-CESSATION AID

Reliable data on the efficacy of e-cigarettes as a smoking-cessation aid are limited. Surveys and observational studies, which are inherently subject to reporting bias and confounding, have yielded conflicting results.<sup>17-20</sup> Few randomized



**Figure 1. Typical Second-Generation E-Cigarette.**

Second-generation e-cigarettes are equipped with a “clearomizer” — a clear tube that contains the heating-coil assembly. In this example, silica fiber wicks, which hang freely in the e-liquid within the clearomizer, transport the e-liquid by means of capillary action into the heating coil. (In another design, the wicks reside only inside the heating-coil assembly.) Users can refill the clearomizer with a liquid of their choice, an option that was generally not available in first-generation e-cigarettes. When power is applied, e-liquid is vaporized at the heating coil and condenses to an aerosol as it is drawn through a tube from the heating coil and inhaled through the mouthpiece.

clinical trials on the use of e-cigarettes for smoking cessation have been published to date. In one 12-month, randomized trial that was designed to assess smoking reduction and abstinence in

300 smokers who did not intend to quit, a popular Italian e-cigarette that delivered nicotine at two strengths (7.2 mg and 5.4 mg per milliliter) was compared with an e-cigarette that did not deliver nicotine. The reduction in the number of conventional tobacco cigarettes smoked per day did not differ significantly between groups.<sup>21</sup> A small randomized trial among conventional cigarette smokers showed that using an e-cigarette reduced craving during short-term abstinence from smoking to a degree similar to that of smoking a conventional cigarette. In this study, cigarette smokers who were randomly assigned to receive e-cigarettes with instructions to use them as often as they wished smoked significantly fewer conventional cigarettes over the ensuing 8 weeks than smokers who did not receive e-cigarettes.<sup>22</sup> Another small randomized trial of short duration that involved young adults who were not necessarily contemplating smoking cessation showed that at 3 weeks participants who received nicotine e-cigarettes were smoking fewer conventional cigarettes per day than participants who received nicotine-free e-cigarettes.<sup>23</sup>

In the largest clinical trial to date, 657 smokers in New Zealand were randomly assigned to receive nicotine e-cigarettes (with cartridges containing 10 to 16 mg of nicotine per milliliter), nicotine patches, or non-nicotine e-cigarettes. At 6 months, the verified quit rates were 7.3% with nicotine e-cigarettes, 5.8% with nicotine patches, and 4.1% with non-nicotine e-cigarettes — differences that were not statistically significant. The trial showed that dual use of tobacco cigarettes and e-cigarettes persisted at 6 months at moderately high levels (approximately one third of participants); dual use also occurred among patch users but at lower levels (7%). Abstinence rates were substantially lower than anticipated, which reduced the statistical power to detect differences among the groups.<sup>24</sup>

The efficacy of e-cigarettes as a smoking-cessation intervention remains uncertain owing to the limited data available from randomized trials.<sup>25</sup> Furthermore, it is difficult to extrapolate the results of studies that used first-generation e-cigarettes to second- and third-generation devices that are more satisfying to users because of changes in aerosol characteristics, nicotine delivery, and the variety of flavors. Recent meta-analyses that have combined data from randomized trials and observational cohort studies have

not shed further light on the efficacy of e-cigarettes as a smoking-cessation aid.<sup>26,27</sup>

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POTENTIAL POSITIVE  
AND NEGATIVE HEALTH EFFECTS  
OF E-CIGARETTE USE

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The documented and potential health effects of e-cigarette use should be considered in the context of whether the devices are being used in the short term as a cessation aid for tobacco smoking, as a long-term alternative to tobacco smoking, or as a product that nonsmokers of tobacco perceive as less deleterious to health than tobacco cigarettes. In the case of the last use listed, even small risks of adverse health effects may be unacceptable and warrant efforts to curtail use. As a smoking-cessation aid or an alternative to tobacco use, however, the risks of e-cigarette use should be compared with those associated with the use of conventional cigarettes and with FDA-approved smoking-cessation treatments, such as nicotine-replacement products, varenicline, and bupropion. As noted above with regard to the value of smoking-cessation studies, the evolution of e-cigarette technology complicates research on the comparative safety of these products.

#### CONSTITUENTS OF LIQUIDS AND AEROSOLS

Simply stated, the e-cigarette aerosolization process involves heat generated by electric current as it flows through a wire that surrounds a wick saturated with liquid. The composition of the aerosol that is generated depends on the ingredients of the liquid, the electrical characteristics of the heating element, the temperature reached, and the characteristics of the wick. As stated at the beginning of the article, e-cigarette liquids generally consist of vegetable glycerin (also called glycerol), propylene glycol, or a mixture of the two; nicotine in a concentration from 0 to 24 mg per milliliter; and flavorings. Vegetable glycerin and propylene glycol, along with many of the flavorings included in e-cigarette liquids, are commonly used as food additives and are considered to be safe for oral ingestion; however, data on the safety of long-term inhalation of these substances are limited to studies in animals (e.g., a study in rodents of inhaled glycerol that led to the development of localized, mild squamous metaplasia of the upper airways<sup>28</sup>), are based on exposures that are quite different from

those associated with e-cigarettes (e.g., upper and lower respiratory symptoms and reduced lung function associated with exposure to the propylene glycol in theatrical smokes and fogs<sup>29</sup>), or are unavailable (e.g., because many flavorings have not been analyzed).

Analyses of commercially available e-cigarette liquids and aerosols with the use of gas or liquid chromatography coupled to mass spectroscopy have revealed the presence of constituents other than the listed ingredients (Table 1).<sup>30-37</sup> These compounds were generally found in concentrations lower than those associated with toxicity in foods or oral pharmaceuticals, although some products have had high enough levels to raise concerns about safety.<sup>30</sup> One study showed that e-cigarette liquids from a particular manufacturer contained higher levels of ethylene glycol than glycerol or propylene glycol, which was probably a reflection of inappropriate manufacturing practices; ethylene glycol has not been approved for use in any product intended for human consumption.<sup>38</sup>

Many of the liquid flavorings in e-cigarettes are aldehydes, which in some cases are present in concentrations sufficient to pose risks owing to the irritant characteristics of these compounds.<sup>39</sup> Sweet-flavored e-cigarette liquids often contain diacetyl, acetyl propionyl, or both.<sup>40</sup> These flavorings are approved for use in foods but have been associated with respiratory disease when inhaled during manufacturing processes.<sup>41</sup> Some e-cigarette liquids are flavored with tobacco extracts, and these may contain tobacco-specific nitrosamines, nitrates, and phenol,<sup>42</sup> although in far lower concentrations than those found in tobacco products.<sup>42</sup>

The constituents of the aerosol generated by e-cigarettes<sup>33-37</sup> (Table 1) and inhaled by the user are more directly relevant to health than the ingredients of e-cigarette liquids. The nicotine contained in the aerosol from 13 puffs of an e-cigarette in which the nicotine concentration of the liquid is 18 mg per milliliter has been estimated to be similar to the amount in the smoke of a typical tobacco cigarette, which contains approximately 0.5 mg of nicotine.<sup>33</sup> The concentration of formaldehyde inhaled in mainstream e-cigarette aerosol has been estimated to be approximately 400  $\mu$ g per cubic meter in a typical second-generation e-cigarette. This concentration is greater than the 30-minute short-term average

**Table 1. Constituents of Liquids and Aerosols in E-Cigarettes.**

**Liquids<sup>30-32</sup>**

Listed ingredients

Glycerol  
Propylene glycol  
Nicotine

Other compounds detected

Acetone  
Acrolein  
1,3-Butadiene  
Cyclohexane  
Diethylene glycol  
Ethylene glycol  
Ethanol  
Formaldehyde  
Tobacco alkaloids (nornicotine, myosmine, and anabasine have been detected in some products, although tobacco was not listed as an ingredient)

**Aerosols<sup>33-37</sup>**

Listed ingredients

Glycerol  
Propylene glycol  
Nicotine

Other compounds detected

Acetaldehyde  
Acetone  
Acrolein  
Formaldehyde  
N'-nitrosonornicotine (NNN)  
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)  
Metals (cadmium, lead, nickel, tin, copper)  
Toluene

limit for continuous exposure that was established to prevent sensory irritation in the general population,<sup>33</sup> although intermittent and continuous exposures cannot be compared directly. Although the concentration of carbonyl compounds such as formaldehyde found in e-cigarette aerosol is substantially lower than that in the smoke from tobacco cigarettes, this concentration is elevated when the voltage used to generate the aerosol is elevated (4.8 to 5.0 V vs. 3.0 V).<sup>43,44</sup> However, it has been argued that this high-voltage scenario is not realistic because the aerosol generated in a laboratory by means of coil



overheating is so harsh that it would be avoided by users.<sup>45</sup> Another laboratory study showed that e-cigarette aerosol and the smoke from tobacco cigarettes contained similar amounts of reactive oxygen species and that the size of the particles distributed in e-cigarette aerosol was in the respirable range that leads to small-airway or alveolar deposition, with a mass median aerodynamic diameter of 1.03  $\mu\text{m}$ .<sup>37</sup> However, the composition of the particles in e-cigarette aerosol differs from that of the particles in tobacco smoke and outdoor air pollution.

Overall, studies of potentially toxic substances in e-cigarette aerosol have shown that a number of such substances are present, including some known or suspected carcinogens, such as formaldehyde and acetaldehyde, although these compounds are found in substantially lower concentrations in e-cigarette aerosol than in the smoke from tobacco cigarettes when excess voltage in e-cigarettes is avoided. There is a large degree of variability in user exposure to these aerosol constituents across devices, e-cigarette liquids, and patterns of e-cigarette use.

#### BIOLOGIC EFFECTS IN IN VITRO SYSTEMS AND IN VIVO STUDIES IN ANIMALS

Research on the biologic effects of e-cigarette liquids and aerosols is still nascent. The data that are currently available allow for an estimation of the potential risks of e-cigarette adoption by nonsmokers and of the potential for risk reduction among persons who switch from tobacco cigarettes to e-cigarettes. Some investigators have approached this issue by exposing cell cultures to liquids, aerosol extracts, or aerosols from e-cigarettes<sup>46-56</sup> (Table 2). The heterogeneity of the in vitro systems and e-cigarette products used in these studies makes it difficult to synthesize the findings, but it appears that e-cigarette aerosols can have biologic effects on a variety of human cell types, including airway epithelium and lung endothelium, with some direct comparison studies suggesting that e-cigarettes may be less toxic to cells than tobacco cigarettes.

In vivo studies in animals can provide insights into the biologic effects of exposure to e-cigarette aerosol that cannot be studied in humans. However, the relevance of the findings from animal studies to human health must be considered with caution given the differences in species and in the comparability of the doses

and the timing of exposure in laboratory animals with actual human exposure. In addition, none of the studies initially exposed animals to smoke from tobacco cigarettes and then randomly assigned them either to continued exposure to tobacco smoke or to e-cigarette aerosol in order to obtain insights into the biologic effects of switching from tobacco to e-cigarettes.

The short-term exposure of mice to the inhalation of nebulized, nicotine-containing liquid from e-cigarettes was associated with lung inflammation and systemic and pulmonary oxidative stress accompanied by alterations in the functioning of the endothelial barrier of the lung.<sup>57</sup> In another study, mice exposed to e-cigarette aerosol had diminished levels of glutathione, which is critical to maintaining cellular balance in oxidation–reduction reactions, and increased levels of proinflammatory cytokines in the lungs.<sup>58</sup> A third study in mice revealed that short-term exposure to cigarette smoke caused lung injury characterized by albumin leak, oxidant stress, and apoptosis that did not occur after exposure to e-cigarette aerosol.<sup>59</sup> In a study comparing mice that were exposed to e-cigarette aerosol for 4 weeks with mice that were not exposed, exposed mice had higher levels of inflammatory cytokines in bronchoalveolar lavage fluid than unexposed mice.<sup>56</sup> In a study in mice in which allergic airway disease was induced by sensitization and re-exposure to ovalbumin, the intratracheal instillation of e-cigarette liquid containing nicotine led to increases in airway inflammation, airway hyperresponsiveness, and the production of Th2 cytokines and ovalbumin-specific IgE.<sup>60</sup>

Some in vivo studies suggest mechanisms by which e-cigarettes could increase the risk of respiratory infection. Mice exposed to e-cigarette aerosol for 2 weeks had a statistically significant increase in oxidative stress and moderate macrophage-mediated inflammation.<sup>61</sup> The mice also had significantly impaired pulmonary bacterial clearance as compared with mice exposed only to ambient air after intranasal infection with *Streptococcus pneumoniae*, an effect that was due partially to reduced phagocytosis by alveolar macrophages. In response to infection with the influenza A virus, the mice exposed to e-cigarette aerosol had higher viral titers in the lungs and higher rates of virus-induced illness and death than the unexposed mice. In a study of pneumonia in mice,<sup>56</sup> ex vivo exposure of *Staphy-*

**Table 2. In Vitro Studies of the Biologic Effects of E-Cigarette Liquids and Aerosols.**

Study	Exposure to E-Cigarettes	Cell Type	Key Findings	Exposure to Tobacco Smoke or Tobacco-Smoke Extract
Misra et al. <sup>46</sup> *	Liquid, pad-collected aerosol	Human alveolar epithelial cell line, hamster ovary cell line, Ames bacterial mutagenicity assay	No cytotoxic, mutagenic, genotoxic, or inflammatory effects	Cytotoxic, mutagenic, genotoxic, and inflammatory effects from smoke
Wu et al. <sup>47</sup>	Nicotine-free liquid	Primary human airway epithelial cells	Increased production of interleukin-6, increased susceptibility to human rhinovirus infection	Not assessed
Willershausen et al. <sup>48</sup>	Liquid	Human periodontal ligament fibroblasts	Reduced proliferation	Not assessed
Bahl et al. <sup>49</sup>	Liquid	Human embryonic stem cells and pulmonary fibroblasts, mouse neuronal stem cells	Cytotoxicity, with stem cells more susceptible than differentiated fibroblasts	Not assessed
Romagna et al. <sup>50</sup>	Aerosol extract added to medium	Mouse fibroblast cell line	Cytotoxicity caused by 1 of 21 extracts	Substantially greater cytotoxic effects from extract
Farsalinos et al. <sup>51</sup>	Aerosol extract added to medium	Cardiomyoblast cell line	Cytotoxicity with flavored extracts but not with unflavored extracts	Substantially greater cytotoxic effects from extract
Rubenstein et al. <sup>52</sup>	Aerosol extract added to medium	Rat hepatic Kupffer cell line	Inflammatory response, oxidative stress, cytokine release	Similar effects from extract
Cervellati et al. <sup>53</sup>	Aerosol above culture medium	Human alveolar epithelial and keratinocyte cell lines	Decreased cell viability only if flavoring and nicotine included	Similar effects from smoke
Neilson et al. <sup>54</sup> *	Aerosol (cells at air-liquid interface)	Primary human bronchial epithelial cells	No effect on cell viability	Substantial effects from smoke on cell viability
Scheffler et al. <sup>55</sup>	Aerosol (cells at air-liquid interface)	Primary human bronchial epithelial cells	Reduced cell viability, increased oxidative stress	Greater effects on cell viability and oxidative stress from smoke
Hwang et al. <sup>56</sup>	Aerosol (cells at air-liquid interface)	Human alveolar epithelial and keratinocyte cell lines and human alveolar macrophages	Dose-dependent epithelial-cell death, reduced antimicrobial activity of macrophages	Not assessed
Schweitzer et al. <sup>57</sup>	Liquid and aerosol extract	Primary human lung endothelial cells	Loss of endothelial barrier function, apparently caused at least in part by nicotine	Similar effects from smoke

\* This study was funded by the tobacco industry.

*lococcus aureus* bacteria to an extract of e-cigarette aerosol resulted in a more virulent infection, possibly by inducing biofilm formation, invasiveness, and resistance to antimicrobial peptides.

In a study relevant to exposure in early life, neonatal mice were exposed to e-cigarette aerosol with or without nicotine or to ambient air during the first 10 days of life.<sup>62</sup> Mice exposed to the e-cigarette aerosol with nicotine gained less weight during the first 10 days of life than mice exposed only to ambient air. Even after adjustment for body weight, the nicotine-exposed mice had modestly impaired lung growth as compared with control mice. In a study of human embryonic stem cells and of cardiac development in zebrafish, both e-cigarette aerosol and tobacco smoke had some adverse effects on development, but the degree of toxicity and the spectrum of developmental defects were greater with tobacco smoke.<sup>63</sup>

#### EFFECTS ON HUMAN HEALTH

For long-term smokers who are unable to give up cigarette smoking altogether, it is speculated that the use of e-cigarettes rather than tobacco cigarettes may be associated with better short-term and long-term health outcomes, but clinical and epidemiologic data on health outcomes are not yet available. Two potential hazards related to e-cigarettes are acute toxic effects caused by accidental or intentional ingestion of e-cigarette liquids and physical injury caused by the e-cigarette device. Ingestion of e-cigarette liquids by young children has been reported with increasing frequency,<sup>64</sup> and although the manifestations of nicotine toxicity — such as nausea, vomiting, headache, and dizziness — are usually mild,<sup>65</sup> the ingestion by a child of a full 10-ml or 20-ml bottle of nicotine-containing e-cigarette liquid may be lethal.<sup>66</sup> A fatal intentional overdose of e-cigarette liquid by means of oral ingestion has been reported in a 24-year-old woman.<sup>67</sup> There have been rare instances of injury caused by the explosion of an e-cigarette device,<sup>68</sup> but it is not clear whether such events resulted from inappropriate use.

Although nicotine-free e-cigarette liquids are available, the use of liquids containing nicotine is much more common. Nicotine has been approved by the FDA for use in smoking cessation in oral form (as gum or a lozenge), transdermal form, and inhaled form (in nasal spray or an oral

inhaler) but not in the form of an e-cigarette. Nicotine is addictive, and the use of e-cigarettes by persons who do not use tobacco clearly has the adverse effect of promoting nicotine addiction. Beyond its addictive properties, short-term or long-term exposure to nicotine in adults has not been established as dangerous.<sup>69</sup> Nicotine may have side effects, including gastrointestinal symptoms, headache, palpitations, and local irritation of the skin or oral cavity,<sup>70</sup> but in a meta-analysis of trials of nicotine-replacement therapy, only nausea appeared to be slightly more common with active therapy than with placebo.<sup>71</sup> Epidemiologic studies of health outcomes associated with the use of snus, a moist, Swedish-style version of snuff that delivers nicotine, have revealed no association with the incidence of cancer or myocardial infarction, although associations with death from myocardial infarction and with heart failure have been suggested in individual studies of snus.<sup>72</sup>

Epidemiologic studies indicate that prenatal maternal smoking is associated with adverse cognitive and behavioral consequences for the child<sup>73</sup>; these adverse effects can also be seen in association with smoking during adolescence, a period of developmental vulnerability. Data from studies in animals suggest that the neurotoxic effects of nicotine on the developing brain may play a role in these associations.<sup>74,75</sup> Although all nicotine should be avoided during pregnancy, a large randomized trial of nicotine-replacement therapy versus placebo for pregnant smokers, in which both groups were provided with behavioral support, showed that nicotine-replacement treatment led to reduced smoking in the second trimester and, subsequently, better child development outcomes at 2 years of age.<sup>76</sup> The adverse effects of prenatal exposure to nicotine on lung development have been observed in studies of humans and nonhuman primates.<sup>73</sup> In adolescence, nicotine exposure may have effects on the brain that increase susceptibility to dependence on cocaine and other illicit drugs.<sup>77</sup>

The physiological effects of e-cigarette use may be less harmful than those of tobacco smoking. A tobacco-industry study showed that the acute increases in heart rate and blood pressure that followed tobacco-cigarette use were greater than those that followed e-cigarette use.<sup>78</sup> Switching from tobacco smoking to e-cigarette use did not appear to be associated with any elevation of

blood pressure over 52 weeks, and blood pressure may decline with successful cessation of tobacco smoking.<sup>79</sup> Tobacco smoking has been reported to cause an acute delay in myocardial relaxation and an increase in arterial stiffness that are not observed after e-cigarette use.<sup>80,81</sup> E-cigarettes have been reported to cause some subtle, acute changes in pulmonary function,<sup>82</sup> but the effects of use on lung function may not be as great as those associated with tobacco cigarettes.<sup>83</sup> A small, uncontrolled study of persons with asthma who were followed for 24 months after switching from conventional cigarettes to e-cigarettes has suggested that lung function may improve and asthma symptoms may decrease after the switch to e-cigarettes.<sup>84</sup> Active and passive exposure to tobacco smoke has been observed to increase total blood counts of leukocytes, granulocytes, and lymphocytes, an effect not observed after similar exposure to e-cigarettes.<sup>85</sup> However, the relevance of these findings to future health is uncertain given the absence of data that directly address the long-term effects on health outcomes of e-cigarette use versus the use of conventional tobacco products or the use of neither product.

## CONCLUSIONS

It is clear that the use of e-cigarettes has biologic effects and possibly health-related effects on persons who do not smoke conventional tobacco products. Although some studies suggest that

smoking e-cigarettes may be less dangerous than smoking conventional cigarettes, more needs to be learned. A particular challenge in this regard is the striking diversity of the flavorings in e-cigarette liquids, since the effects on health of the aerosol constituents produced by these flavorings are unknown. At present, it is impossible to reach a consensus on the safety of e-cigarettes except perhaps to say that they may be safer than conventional cigarettes but are also likely to pose risks to health that are not present when neither product is used. Epidemiologic data indicate that e-cigarette use is growing among minors and young adults and may promote nicotine addiction in these age groups among those who would otherwise have been nonsmokers. More research is needed to understand the effectiveness of e-cigarettes as a smoking-cessation tool, to identify the health risks of e-cigarette use, and to make these products as safe as possible. Even as this research is under way, regulations that make e-cigarettes unavailable to children is warranted,<sup>86</sup> as are public health initiatives that discourage nonsmokers from smoking conventional cigarettes or using e-cigarettes.

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