Harms of Electronic Cigarettes: What the Healthcare Provider Needs to Know

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Abstract

Electronic cigarettes (e-cigarettes) reached the market without either extensive preclinical toxicology testing or long-term safety trials that would be required of conventional therapeutics or medical devices. E-cigarettes are considered a tobacco product and as such have no manufacturing quality or safety standards. A growing body of evidence documents severe harms from e-cigarette use, including injuries from product explosions, nicotine poisoning, and severe lung diseases. Commonly used e-cigarette components have significant inhalation toxicity. Emerging evidence from laboratory studies suggests substantial reason for concern for long-term harms, including risk for cardiovascular disease, chronic obstructive lung disease, and cancer. Rather than helping people stop smoking, e-cigarette use is associated with reduced rates of smoking cessation among current smokers and an increased risk of relapse to smoking among former smokers. The World Health Organization advises, "Unlike the tried and tested nicotine and non-nicotine pharmacotherapies that are known to help people quit tobacco use, WHO does not endorse e-cigarettes as cessation aids." Careful evaluation of all the available research justifies a strong recommendation that healthcare providers should neither prescribe nor recommend e-cigarettes for persons who are tobacco dependent. If a patient is dependent on e-cigarettes, the healthcare provider should provide counseling and treatment (of nicotine dependence) to help the patient to stop their e-cigarette use.

Keywords: electronic cigarettes; toxicity; nicotine dependence; tobacco dependence treatment; guidelines

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Electronic cigarettes (e-cigarettes) have been promoted as less harmful than combustible tobacco use and as a potential treatment for tobacco dependence. E-cigarettes reached the market without either extensive preclinical toxicology testing or long-term safety trials that would be required of conventional therapeutics or medical devices. There are currently neither manufacturing standards nor regulations on the contents of e-cigarette products. E-cigarettes are considered a tobacco product, contain substances that have known pulmonary toxicity, and are not U.S. Food and Drug Administration (FDA) approved for the treatment of any disease. The tobacco industry has a long history engineering their products to be more addictive, of claiming products had reduced harm although they did not (such as low tar cigarettes), and of designing and promoting products in ways to appeal to young people (1).

A growing body of evidence documents toxicity of e-cigarette components and severe harms from e-cigarette use and suggests that rather than helping people stop smoking, their use is associated with reduced rates of smoking cessation. Effects of long-term use is not yet known; however, laboratory studies document substantial reasons for concern about long-term harms.

Catastrophic Harms Caused by E-Cigarette Use

Catastrophic harms of e-cigarette use have been repeatedly reported. Unlike FDA-approved medications, there are no

ingredient or manufacturing quality standards for e-cigarettes. Case reports and case series describe burns and severe facial injuries (from product explosions) (2–5), epiglottitis (6), acute nicotine poisoning (7–9), seizures (10), liver injury (11), and severe lung disease, including eosinophilic pneumonia (12, 13), diffuse alveolar hemorrhage (14), hypersensitivity pneumonitis (15, 16), organizing pneumonia (17), lipoid pneumonia (18–20), and severe asthma (21). The Centers for Disease Control has identified many cases of e-cigarette or vaping product use–associated lung injury (EVALI) leading to hospitalization and death. Although most of the cases were associated with use of tetrahydrocannabinol-containing products and believed to be from the use of vitamin E acetate in those products, 29% of fatal cases and 14% of all reported cases describe the exclusive use of nicotine-containing e-cigarette products (22). There have been recently published case reports of patients with severe EVALI who did not use tetrahydrocannabinol-containing e-cigarette products (23).

Commonly used flavoring agents are known to be harmful when inhaled. Diacetyl (2,3-butanedione) is an artificial flavor used to give butter-like flavor to food products and is known to cause obliterative bronchiolitis when inhaled during occupational exposure (24). *In vitro* studies using human-derived tracheal/bronchial epithelial cells demonstrated that exposure to diacetyl vapors induces airway epithelial injury (25). Diacetyl and the closely related compounds 2,3-pentanedione and acetoin are commonly found in e-cigarette products, even those labeled as being diacetyl free (26).

Cardiovascular Impacts

Analyses of National Health Interview Survey data found that daily e-cigarette use was associated with increased odds of having a myocardial infarction (adjusted odds ratio [aOR], 1.79; 95% confidence interval [CI], 1.20–2.66) (27). A systemic review identified 38 experimental studies; the 90% of those studies that were deemed to be without conflicts of interest demonstrated potentially harmful cardiovascular effects. Human studies showed increased heart rate, blood pressure, and arterial stiffness. A study in mice demonstrated increase in atherosclerotic plaque after e-cigarette vapor exposure. *In vitro* studies identified disordered endothelial cellular structure and function, increased reactive oxygen species, and vascular inflammatory markers (28, 29).

Respiratory Impacts

Findings from the California Children's Health Study demonstrated increased risk for bronchitis symptoms (daily cough, congestion, or phlegm) among current e-cigarette users who were never (combustible tobacco) smokers (odds ratio [OR], 1.70; 95% CI, 1.11–2.59) (30). Adult (⩾18 yr) data from the 2013 to 2018 PATH (Population Assessment of Tobacco and Health) survey found that current and former e-cigarette use was associated with incident respiratory disease, including chronic bronchitis (aOR, 1.33; 95% CI, 1.07–1.67), emphysema (aOR, 1.69; 95% CI, 1.15–2.49), and asthma (aOR, 1.31; 95% CI, 1.01–1.71) Restricting analyses to those reporting good health or better at baseline, current e-cigarette use continued to be associated with incident respiratory disease on follow-up (aOR, 1.43; 95% CI, 1.14–1.80) (31).

Biologic plausibility of e-cigarettes causing emphysema is supported by studies in mice that demonstrate pathologic changes of increased mucus production, increased apoptosis within alveoli and airway epithelium, and airspace enlargement after 4 months of nicotine-containing e-cigarette aerosol exposure (32).

Biologic plausibility of e-cigarette use causing bronchitic symptoms is supported by findings demonstrating reduction in lung defenses from e-cigarette aerosol exposure. Exposure of lung microvascular endothelial cells to e-cigarette aerosols disrupts endothelial barrier function (33). A randomized study of occasional (human) smokers comparing sham vaping, vaping propylene glycol/glycerin without nicotine, and vaping propylene glycol/glycerin with nicotine found that compared with sham vaping, vaping with or without nicotine increased serum club cell protein 16, which is a marker of epithelial dysfunction (34). In sheep, tracheal mucus velocity is decreased after inhalation of propylene glycol plus vegetable glycerin aerosol (35). Mice exposed to e-cigarette aerosols for 2 weeks and then inoculated intranasally with *Streptococcus pneumoniae* had an increased intrapulmonary bacterial burden and decreased bacterial phagocytosis by alveolar macrophages. E-cigarette aerosol–exposed mice inoculated with a mouse adapted H1N1 influenza virus had elevation of both infectious viral titers and mortality (36).

Cancer Risk

The e-cigarette epidemic is of relatively recent onset, and the development of cancer can take many years, and thus in assessing cancer risk, we need to look to laboratory studies. Carcinogenic substances that are linked to bladder cancer have been shown to accumulate in the urine of human e-cigarette users (37). A study of mice exposed to e-cigarette emissions (4 h/d, 5 d/wk) for 54 weeks found lung adenocarcinoma in 9 of 40 mice with e-cigarette exposure compared with only 1 of 40 unexposed mice ($P = 0.02$); hyperplastic changes to the bladder urothelium were evident in 23 of the e-cigarette–exposed mice but only one of the nonexposed mice ($P < 0.001$) (38). Biologic plausibility is supported by findings of higher amounts of DNA adducts and reduced nucleotide excision repair and base excision repair activity in the lung tissue of e-cigarette emission–exposed mice (39).

Other Mechanisms of Injury from E-Cigarette Use

Other toxicities of e-cigarette aerosols include oxidative stress, cytotoxicity, and DNA damage (40). The impact of e-cigarettes on oxidative stress and cytotoxicity is demonstrated by cell culture studies showing increased production of inflammatory cytokines and reduced cell viability from the both the vehicle (propylene glycol/vegetable glycerin) and flavoring agents used in e-cigarettes (41–44). Exposure of human stem cell–derived endothelial cells to e-cigarette liquids increased oxidative stress and had cytotoxic effects that varied by flavor (45). Mice exposed to nicotine-containing e-cigarette emissions for 3–6 months had increased concentrations of inflammatory cytokines and increased amounts of fibrosis in the kidneys, heart, and liver (46).

Dual Use Is Associated with Increased Morbidity

Most smokers who use e-cigarettes remain dual users of combustible tobacco and

e-cigarettes. Dual use exposes the user to the toxins in combustible tobacco and to additional toxins unique to e-cigarettes. Analyses of PATH study data from 2013 to 2016 found a higher rate of incident respiratory disease among dual users of combustible tobacco and e-cigarettes (OR, 2.56; 95% CI, 1.92–3.41) (47). Analyses of data from the Health eHeart study found that dual users smoked a slightly higher number of combustible cigarettes per day, had worse general health scores, and had worse scores on breathing difficulty in the past month compared with cigarette-only users (48). Analysis of data from the 2016–2017 Behavior Risk Factor Surveillance System found that compared with cigarette-only users, dual users of combustible and e-cigarettes had greater odds of stroke (aOR, 1.83; 95% CI, 1.06–3.17) (49).

E-Cigarettes and Cessation of Combustible Tobacco Use

A 2015 Cochrane review combined data from two randomized clinical trials of 12 weeks of e-cigarettes with nicotine versus those without nicotine, neither of which showed statistically significant results individually but when combined, there was a small cessation benefit from nicotine-containing electronic cigarettes (9% vs. 4%) (50). The authors commented that "the small number of trials, low event rates and wide confidence intervals around the estimates mean that our confidence in the result is rated 'low'." A recent randomized clinical trial of 11 weeks of nicotine-containing versus non–nicotine-containing e-cigarettes in smokers with high motivation to stop smoking found no difference in cessation rates (25.4% vs. 23.4%; $P = 0.7$) (51).

An unblinded randomized clinical trial in the United Kingdom compared the provision of e-cigarettes with the prescription of nicotine replacement therapy. Approximately one-quarter of subjects in the study had a copay for the nicotine replacement therapy. Adherence to daily use of nicotine replacement was much lower than that for e-cigarettes. The rate of sustained abstinence from combustible tobacco at 1 year was 18% in the e-cigarette group versus 10% in the prescription for nicotine replacement group ($P < 0.001$); however, among those abstinent from combustible tobacco, 80% of those in the e-cigarette group were still using e-cigarettes at 1 year compared with only 9% of those who achieved abstinence with nicotine replacement therapy. Twenty-two percent of those in the e-cigarette group remained dual users of e-cigarettes and combustible tobacco (52). These results suggest that at best, e-cigarettes substitute one tobacco product for another.

Real-world observational studies of e-cigarettes suggest that rather than treating tobacco dependence, e-cigarette use perpetuates it. Analysis of data from the 2014 Eurobarometer survey of 28 European Union countries found that among 13,019 ever-smokers, history of e-cigarette use was associated with a lower rate of being a former smoker (aOR, 0.43; 95% CI, 0.32–0.58) (53). A meta-analysis of 20 studies, including cohort studies, cross-sectional studies, and clinical trials, found lower odds of stopping smoking among e-cigarette users (OR, 0.72; 95% CI, 0.57–0.91) (54). A study of 6,526 patients who completed a tobacco dependence treatment program with behavioral counseling and nicotine replacement therapy found lower rates of smoking cessation among e-cigarette users at 3-month follow-up (OR, 0.64; 95% CI, 0.56–0.74) (55). A longitudinal study of adult smokers found that the odds of stopping smoking were lower among e-cigarette users even after adjustment for Fagerstrom nicotine dependence score at baseline (OR, 0.8; 95% CI, 0.57–1.02) (56). In a study of 1,357 hospitalized adult smokers who planned to stop smoking, those who used e-cigarettes were less likely to have stopped smoking at 6 months. (10.1% vs. 26.6%; $P < 0.0001$) (57). Among former smokers, e-cigarette use is associated with a greater rate of relapse to combustible cigarette smoking (aOR, 1.70; 95% CI, 1.25–2.30) (58).

The very large sample sizes and repeated demonstrations of similar findings in different populations argue for the validity and generalizability of the findings. Smokers who also use e-cigarettes are less likely to stop smoking, and if they do stop smoking, they are more likely to relapse.

E-Cigarettes and Youth

E-cigarette use among adolescents is epidemic. According to the U.S. National Youth Tobacco Survey, rates of e-cigarette use among high-school students went from 1.5% in 2011 to 27.5% in 2019 (59). A meta-analysis of seven studies including 8,168 participants 14–30 years of age found that the probabilities of cigarette smoking initiation were 23.2% for those with a history of e-cigarette use and 7.2% for those who never used e-cigarettes (aOR, 3.50; 95% CI, 2.38–5.16) (60). Analysis of data from the PATH waves 1 (2013–2014) and 2 (2014–2015) found that among youth who smoked at least one cigarette puff but not more than 100 cigarettes, those who also reported ever-use of electronic cigarettes at wave 1 were more likely to have become established combustible tobacco smokers by wave 2 (19.3% vs. 9.7%; $P < 0.001$) (61).

There is substantial evidence supporting the role of nicotine as a gateway drug to other drug abuse (62, 63). An analysis of Korean Youth Risk Behaviors survey found that most of the individuals with alcohol or drug abuse also reported ever-use of combustible tobacco and/or e-cigarettes (64). A systemic review of studies examining e-cigarette and marijuana use among youth demonstrated that odds of marijuana use was higher in youth who had a history of e-cigarette use (65). A survey of adolescents in Northwest England found e-cigarette use to be associated with alcohol abuse (66). Biologic plausibility of nicotine's function as a gateway drug is supported by studies showing that mice pretreated with nicotine find cocaine more rewarding (67).

Stealth E-Cigarettes: Designed for Use Where Use Is Prohibited

E-cigarette products specifically designed for use where use is prohibited, such as at school or on airplanes, are becoming more popular. One very popular product (JUUL) is designed to look like a flash drive for a computer. Other products on the market are designed to look like pens, hoodies, key fobs for an automobile, and even asthma inhalers. Some of the products specifically advertise their ability to be discreetly used where their use is prohibited (68, 69).

Discussion

E-cigarettes are not a safe product. As an as yet largely unregulated product, e-cigarettes have no manufacturing or safety standards. E-cigarette products usually contain propylene glycol/vegetable glycerin plus

flavoring agents plus nicotine or nicotine salts (70). Heating of the solution leads to the generation of additional toxins and carcinogens. E-cigarette use has caused severe injuries from product explosions, nicotine poisoning, and severe lung diseases.

Laboratory animal and toxicology research suggests substantial probability of additional harms from long-term use, including chronic obstructive lung disease, cardiovascular disease, and cancer. Increased susceptibility to viral and bacterial respiratory infections demonstrated in laboratory animal models is of concern in this time of coronavirus disease (COVID-19) pandemic. Recently published findings from a nationally representative online survey of adolescents found self-reported COVID-19 infection to be more common among e-cigarette users than among nonusers, raising further concern (71).

Accumulating evidence demonstrates that e-cigarette use serves to maintain nicotine addiction and is associated with decreased rates of cessation in smokers and increased rates of relapse to smoking in former smokers. In adolescents, e-cigarettes are introducing a new generation to nicotine and tobacco addiction and prime them for other drug abuse.

In evaluating safety and efficacy of e-cigarettes, one should not restrict analysis to the limited information available from randomized clinical trials. Despite their strengths, randomized clinical trials can have substantial limitations. Findings may not be generalizable outside of the study population. Rare but serious adverse effects may not be detected. Long-term harms cannot be practically assessed (72). The problem of discounting evidence from outside of randomized clinical trials was illustrated by a systemic review of parachute use to prevent death and major trauma related to gravitational challenge that determined that no recommendations could be made because there were no randomized controlled clinical trials (73). Important research raising significant concerns about safety and efficacy of e-cigarette products comes from observational and laboratory studies.

The World Health Organization advises, "Unlike the tried and tested nicotine and non-nicotine pharmacotherapies that are known to help people quit tobacco use, WHO does not endorse e-cigarettes as cessation aids." (74). Careful evaluation of all the available research justifies a strong recommendation that healthcare providers should neither prescribe nor recommend e-cigarettes. Healthcare providers should provide anticipatory guidance against initiating e-cigarette use. For patients who are tobacco dependent and ready to accept treatment, healthcare providers should prescribe or recommend medications that are FDA approved for tobacco dependence treatment (including varenicline, bupropion, transdermal nicotine patch, nicotine polacrilex gum, nicotine lozenge, nicotine nasal spray, and nicotine oral inhaler).

For those smokers who do not wish to use FDA-approved medications for tobacco dependence, we advise that the providers assess readiness to change, review the patient's physical and mental health, and evaluate for any comorbidities that may be resulting in difficulty accepting tobacco dependence treatment. Nonpharmacologic interventions can be considered. A meta-analysis of four randomized clinical trials found mindfulness meditation to be effective and superior to counseling alone (75).

If a patient is dependent on e-cigarettes, it would be unwise for the provider to recommend return to combustible tobacco products. The healthcare provider should provide counseling and treatment to help the patient to stop their e-cigarette use. As the addictive substance in electronic cigarettes is nicotine, it would be reasonable to approach e-cigarette addiction in a manner analogous to that for other tobacco products. Assess readiness to change and barriers to change. Address the social and psychiatric issues that reinforce the e-cigarette product use. Consider prescription or recommendation for medication that is FDA approved for tobacco dependence treatment.

The evidence does not support the use of e-cigarettes as a harm reduction strategy. The European Respiratory Society states that "The tobacco harm reduction strategy is based on well-meaning but incorrect or undocumented claims or assumptions" (76). The chair of the World Health Organization Study Group on Tobacco Product Regulation states that "These products, recently introduced into the global markets, are far from being harmless. The notion of harm reduction is a trap by the tobacco industry trying to perpetuate nicotine addiction" (77). ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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