E-cigarettes and cardiopulmonary health: A review for clinicians

Evan W. Neczypor, BS[1,2], **Matthew J. Mears, BS**[1,2], **Arunava Ghosh, PhD**[3], **M. Flori Sassano, PhD**[3], **Richard J. Gumina, MD, PhD**[4], **Loren E. Wold, PhD**[1,2,*], **Robert Tarran, PhD**[3,*]

[1]Colleges of Nursing and Medicine, The Ohio State University, Columbus, OH

[2]Dorothy M. Davis Heart and Lung Research Institute, Department of Physiology and Cell Biology, College of Medicine, The Ohio State University, Columbus, OH

[3]Department of Cell Biology and Physiology, The University of North Carolina, Chapel Hill, NC

[4]Division of Cardiovascular Medicine, Department of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, OH[3]

Abstract

Electronic cigarettes (e-cigarettes) are battery powered electronic nicotine delivery systems that use a propylene glycol/vegetable glycerin base to deliver vaporized nicotine and flavorings to the body. E-cigarettes became commercially available without evidence regarding their risks, long-term safety, or efficacy for smoking cessation. Recent clinical trials suggest that e-cigarette use with counseling may be effective in reducing cigarette, but not nicotine-dependence. However, meta-analyses of observational studies demonstrate that e-cigarette use is not associated with smoking cessation. Cardiovascular studies reported sympathetic activation, vascular stiffening, and endothelial dysfunction, which are associated with adverse cardiovascular events. To date, the majority of pulmonary clinical trials in e-cigarette users utilized standard spirometry as the primary outcome measure, reporting no change in lung function. However, acute and chronic studies reported increased biomarkers of pulmonary disease in e-cigarette users. While these studies were conducted in adult subjects, >30% of high school-age adolescents reported e-cigarette use. The effects of e-cigarette use on cardiopulmonary endpoints in adolescents and young adults remains unstudied. Due to adverse clinical findings and associations between e-cigarette use and increased incidence of respiratory diseases in people who have never smoked, large longitudinal studies are needed to understand the risk profile of e-cigarettes. Consistent with the Centers for Disease Control and Prevention recommendations, clinicians should monitor the health risks of e-cigarette use, discourage nonsmokers and adolescents from using e-cigarettes, and discourage smokers from engaging in dual use without cigarette reduction or cessation.

Co-corresponding authors: Loren E. Wold, PhD, FAHA, FAPS, Dorothy M. Davis Heart and Lung Research Institute, The Ohio State University, 473 W 12th Avenue, Columbus, OH 43210, Robert Tarran, PhD, Department of Cell Biology and Physiology, The University of North Carolina, 115 Mason Farm Road, Chapel Hill, NC 27599.
*=denotes equal senior authorship

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Introduction

Electronic cigarettes (e-cigarettes; EC) are a new and developing electronic nicotine delivery system that became commercially available in 2004. The long-term cardiopulmonary effects of e-cigarettes remain poorly understood. Thus, maintaining up-to-date knowledge on e-cigarettes is a current challenge for clinicians, especially since e-cigarettes continue to change in engineering design and chemical composition and are often released commercially without clinical safety or smoking cessation efficacy data. E-cigarettes are battery-powered heating elements connected to a tank or reservoir which contains a mixture of nicotine, flavors, and other chemicals dissolved in a propylene glycol/vegetable glycerin vehicle of varying ratios (Figure 1).[1] The first two generations of e-cigarettes were inefficient at increasing plasma nicotine compared to combustible tobacco products. In contrast, high-powered third generation devices achieved similar plasma nicotine levels and pharmacokinetics as tobacco cigarettes (TC).[2] Fourth generation EC devices (e.g. JUUL, PuffBar) switched from freebase nicotine to nicotine salt and benzoic acid in order to compensate for their decreased nicotine delivery efficiency, resulting in a much higher delivery of nicotine.[3] Prior research has indicated that less e-liquid is consumed when using devices with higher nicotine content.[2] Therefore, more efficient nicotine delivery could reduce overall exposure to EC aerosol; however, this has not been directly studied in fourth generation devices relative to older models. Fourth generation EC devices are now readily available in both rechargeable and disposable forms with limited regulations. However, the impact of EC on cardiopulmonary health is incompletely understood.

The Unresolved Issues

First, it has been suggested that e-cigarettes improve smoking cessations rates (this notion has been contested and is discussed in detail later in this review). Therefore, if e-cigarettes are to be used as a transition to stop tobacco cigarette use, understanding the relative harms of e-cigarette use versus tobacco cigarette smoking is vital for clinicians considering e-cigarettes as a potential treatment option for current smokers. On the other hand, the absolute harms of e-cigarettes, including their potential to cause nicotine addiction and encourage cigarette smoking, must be considered when discussing health risks with non-tobacco cigarette smoking patients.

Second, and critically important, the use of e-cigarettes has increased in adolescents[4] (+14.4% from 2017–2019, n = 4,513 12th graders) and young adults[5] (+2.5% from 2014–2018, n = 1,857 aged 18–24). In 2019, self-reported past 30-day use of e-cigarettes was 27.5% in adolescents (grades 9–12, n = 10,097), and 10.5% in early adolescents (grades 6–8, n = 8,837).[6] Notably, the perception of reduced harm associated with e-cigarette aerosol inhalation (vaping) compared to traditional cigarette smoking has contributed to their uptake by people who have never smoked (never-smokers);[7] however, smoking cessation is not

a primary reason for vaping among youth and young adults.[8] Rather, a meta-analysis of longitudinal studies showed that e-cigarette use in adolescents and young adults is associated with subsequent cigarette smoking initiation (OR = 3.62 [95% CI: 2.42–5.41]).[9] Over $110 million was spent on e-cigarette advertising in 2018,[10] which may have contributed to the increased uptake of e-cigarettes.[11] Youth may be influenced by such promotions and develop a receptive attitude toward product use.[12–14] Following a congressional hearing in 2019, the FDA issued a warning regarding youth-facing advertisement strategies employed by JUUL Labs. Subsequently in 2020, the US Food and Drug Administration (FDA) passed legislation to reduce sales of e-cigarettes to underage (less than 18 years old) users, banning the sale of most fourth generation flavored cartridge pods.[15] However, this legislation did not apply to disposable e-cigarettes, which became widespread in the months following. The AHA's positions on EC regulation and long-term goals can be found in this statement.[16]

For clinicians, clarity is required regarding the potential clinical utility of e-cigarettes to aide with tobacco cigarette use, and the potential public health crisis predicated on an increase in youth/young adult nicotine addiction and transition to tobacco cigarette use.[17] As devices continue to evolve and become more palatable, efficient, sleek, and easy to use, smokers may be more likely to transition away from traditional cigarettes. However, these attractive features coincide with youth appeal. Clinicians should balance these perspectives when making individual decisions with their patients and when discussing these devices in health education settings and on media platforms, all of which can affect public opinion and discourse. To assist clinicians in making these decisions, this review will examine the epidemiologic data of e-cigarette use, review the current state of knowledge on the efficacy of e-cigarettes as a smoking cessation tool, and examine the impact of e-cigarettes on cardiopulmonary health.

Search Strategy

PubMed and the Cochrane Central Register of Controlled Trials were searched for English-language studies related to e-cigarettes from January 2012 through November 2020. PubMed "article type" filters were applied to search for controlled clinical trials, randomized controlled trials, meta-analyses, and systematic reviews (see supplement). This search resulted in 384 results which were screened by the authors. Articles were then selected with consideration given to the general medical readership. Reviewing the references of screened articles identified additional observational studies. Additionally, a select few clinical studies, observational studies, and laboratory studies that were not represented in our searches were incorporated (see supplement). Separate, smaller searches were used to identify epidemiological studies and studies related to the E-cigarette or Vaping product use-Associated Lung Injury (EVALI).

Disease Epidemiology

Epidemiological studies on vaping, including meta-analyses, have been performed (Table 1). Associations were reported between e-cigarette use and higher incidence of asthma (OR range = 1.39–3.41 [95% CI range: 1.15–6.49]),[18,19] respiratory disease (OR range = 1.31–2.58 [95% CI range: 1.03–4.89]),[20–22] COVID-19 (OR = 5.05 [95% CI: 1.82–

13.96]),[23] wheeze (OR = 1.67 [95% CI: 1.23–2.15]),[24] and myocardial infarction (OR = 1.79 [95% CI: 1.20–2.66]).[25] Furthermore, dual use of e-cigarettes and cigarettes has been associated with higher rates of cardiovascular disease (OR = 1.36 [95% CI: 1.18–1.56])[26], and cardiovascular risk factors, including metabolic syndrome (OR = 1.57 [95% CI: 1.03–2.40])[27] versus sole cigarette users. Smoking cessation aided by e-cigarettes or other noncombustible nicotine/tobacco products was recently shown to put quitters at increased risk of cardiovascular disease relative to those who quit without use of these alternatives (HR = 1.31 [95% CI: 1.01–1.70]).[28] Due to the novelty of e-cigarettes and the rapidly changing market, these associations (excluding respiratory disease) are derived solely from cross-sectional studies and will require longitudinal surveillance for validation.

E-Cigarettes as a Potential Smoking Cessation Tool - Table 2.

Evaluating the efficacy of e-cigarette use as a smoking cessation strategy is of utmost importance to clinicians. Clinical trials have lagged behind the rapidly evolving e-cigarette market, limiting the bulk of data to outdated first- and second-generation devices. In 2020, a Cochrane Database Systematic Review meta-analysis of 50 clinical trials and intervention studies by Hartmann-Boyce et al.[29] (total n = 12,430) concluded that there is moderate-certainty evidence that electronic cigarettes with nicotine increase smoking cessation rates compared to electronic cigarettes without nicotine (RR = 1.71 [95% CI: 1.00 to 2.92]) and nicotine replacement therapies (NRTs) (RR = 1.69 [95% CI: 1.25 to 2.27]).[29] The most recent update to this e-cigarette Cochrane Systematic Review now includes 56 studies and 12,804 people.[30] The authors conclude with moderate confidence that nicotine e-cigarettes probably do help people to stop smoking for at least six months and probably work better than nicotine replacement therapy and nicotine-free e-cigarettes. However, they also stress the need for more reliable evidence to be confident about the effects of newer e-cigarettes that have greater nicotine delivery.

The duration of cessation is a critical factor that has been examined in other studies. A UK-based trial achieved 1-year smoking abstinence rates of 18% and 9.9% for those provided with second generation e-cigarettes or their choice of standard nicotine replacement therapies (NRTs), respectively (n = 886).[31] All patients also received counseling for a minimum of 4 weeks. Importantly, while e-cigarettes were effective smoking cessation aids, these subjects were much more likely to still be using e-cigarettes (80%) than subjects who were treated with NRTs (9%) after 1 year. Further, 25% of participants in the e-cigarette group became dual users, although dual users in the e-cigarette group experienced greater reductions in cigarette use than dual NRT/cigarette users. These caveats have led other groups to argue against e-cigarette use as first-line treatment option, due to the lack of comparable efficacy in nicotine-cessation and the potential for e-cigarette-induced harm during or after cigarette cessation.[32] A recent Canadian trial (n = 376) using second generation devices found that providing a nicotine-containing e-cigarette with counseling vs counseling alone significantly increased smoking abstinence rates at 12 weeks (21.9% vs 9.1%, respectively), while nicotine-free e-cigarettes did not (17.3%). However, this study did not include an NRT comparison group, and early termination limited statistical power of the trial.[33]

Outside of clinical settings, the effects of vaping on smoking cessation seem less favorable.[34–37] The most recent meta-analysis that included observational studies regarding e-cigarette use and smoking cessation was published in 2021 and utilized studies published through January 2020.[37] This meta-analysis included 55 observational studies and 9 randomized clinical trials. Analysis of clinical trial data corroborated the Hartmann-Boyce et al. review, showing an association between e-cigarette use and smoking cessation (OR = 1.53 [95% CI: 1.16 to 2.02]). However, the observational study data showed that e-cigarette use was not associated with smoking cessation in adult smokers (OR = 0.95; [95% CI: 0.77 to 1.16), nor in a subset of adult smokers who were motivated to quit smoking (OR = 0.85; [95% CI: 0.68 to 1.06). Similar to these meta observational study data, a randomized intervention trial of smokers (n = 6,006) employed by 54 companies found that providing free e-cigarettes alongside standard care (free motivational text messaging and information about the benefits of cessation) was not more effective than other free cessation aids with standard care nor standard care alone.[36] Unlike other randomized trials that provided evidence for e-cigarettes as effective smoking cessation aids,[31,33] this study was not carried out in a clinical setting and participants did not have access to in-person behavioral support.

The apparent dichotomy between the success of clinical trials and lack of efficacy in observational studies may be due in part to the behavioral support and counseling provided during clinical trials. Other variables that may contribute to variable quit rates include nicotine concentration and users' prior experience with vaping, which have both been shown to be significant predictors of success.[38,39] While these referenced studies did not directly assess smoking cessation or nicotine cessation, their findings suggest that training naïve e-cigarette users to properly use their e-cigarettes could improve initial efficacy following clinical recommendations and/or device provision.

Based in part by the evidence reviewed here, the U.S. Preventative Services Task Force has concluded that the data are insufficient to recommend e-cigarettes for smoking cessation in adults.[40] In the 2020 Smoking Cessation: A report of the Surgeon General a comparable conclusion was reached that the evidence is inadequate to infer that e-cigarettes increase smoking cessation.[41] However, the report suggested that the use of e-cigarettes containing nicotine was associated with increased smoking cessation compared with the use of nicotine-free e-cigarettes. E-cigarettes are not currently approved by the FDA as an aid for quitting tobacco cigarette use. Outside of clinical studies, the use of e-cigarettes for smoking cessation is not supported and should not be recommended to patients. Smoking cessation trials using third and fourth generation e-cigarettes that deliver greater amounts of nicotine are needed; studies should include both smoking cessation and nicotine cessation as e-cigarette efficacy endpoints.

Pathophysiology

Clinical study issues—To evaluate the acute effects of vaping, most of the clinical trials assessed in this review used randomized, crossover designs with significant washout periods. Since e-cigarette research is still in its early stages, long-term prospective cohort studies evaluating the risks of chronic use are unavailable. Further, the development of new

e-cigarettes has outpaced the research. The bulk of studies have examined use of first- or second-generation e-cigarettes (see Figure 1), which differ significantly from modern devices in terms of electronic power, nicotine strength, and popularity. The results of trials with these devices may not translate nor be relevant to newer devices that can deliver higher amounts of nicotine. Due to the novelty of e-cigarettes, clinical guidelines and decision-making must be informed by clinical, observational, and laboratory studies.

E-cigarette Impact on the Cardiovascular System - Table 3

<u>Effects of Vaping on Sympathetic Activation of the Cardiovascular System:</u> The effects of vaping on heart rate and blood pressure have been extensively studied. Despite using different e-cigarette device types (generations 1–3), nicotine concentrations, and instructions for user inhalation, 5/7 studies found that vaping with nicotine caused significant acute increases in both heart rate and blood pressure (n = 15–70)[42–48]. Only one study demonstrated significant increases during nicotine-free vaping, and this effect did not persist long after the vaping session.[43] Electrocardiogram measurements revealed that vaping shifted heart rate variability toward sympathetic predominance.[49,50] Collectively, these results suggested that use of nicotine-containing e-cigarettes caused sympathetic activation of the cardiovascular system, which could pose long-term health risks for chronic users, and/or exacerbate pre-existing cardiopulmonary conditions.[51,52]

<u>Effects of Vaping on Vascular Health:</u> Arterial stiffening has been validated as a reliable, independent predictor of adverse cardiovascular outcomes and all-cause mortality.[53] Arterial stiffening contributes to the development of heart failure and is closely linked to atherosclerosis pathogenesis.[54] The rate at which pressure waves propagate through arteries (pulse wave velocity, PWV) is a clinically relevant indicator of arterial stiffness. Several studies showed that acute e-cigarette use increased PWV, with increases ranging from 0.19 m/s to 0.80 m/s (n = 15–70).[42,43,48,55] Significant increases in PWV that were both nicotine-dependent (n = 35)[48] and nicotine-independent (n = 35, n = 31) were detected.[48,55] Due to the rapid timeframe of these trials, increases in PWV are likely the result of sympathetic modulation of smooth muscle tone, and/or endothelial dysfunction (discussed below), as opposed to vascular remodeling.[56,57] A 2020 cross-sectional study (n = 36 e-cigarette users, 285 smokers, and 94 nonuser controls) found that e-cigarette and cigarette users showed no difference in adjusted PWV vs nonusers.[58] However, elsewhere, cigarette use has been associated with increased PWV,[59] highlighting the need for more long-term observational cohort studies with e-cigarette users. Therefore, the effects of chronic vaping on clinically relevant cardiovascular stiffness endpoints remain speculative and will require further study.

Depletion of vasodilatory nitric oxide is a widely accepted driver of endothelial and vascular dysfunction.[60] Several studies reported significant decreases (27–31%) in nitric oxide bioavailability or nitric oxide metabolite concentrations in patient plasma after acute vaping (n = 10–40).[45,61,62] Accordingly, studies also demonstrated reductions in vasodilatory function after acute e-cigarette use.[43,45,55,61] Reductions in stimulated nitric oxide production from e-cigarette user endothelial cells were also observed in a cross-sectional observational study; however, no differences in baseline FMD were reported between groups (n = 36 e-cigarette users, 285 smokers, and 94 nonuser controls).[58] In

addition to reductions in endothelial function, acutely elevated biomarkers of endothelial damage have been observed in patient serum after vaping (n = 10–40).[61,63–65]

Oxidative stress underlies multiple cardiovascular disorders and is known to deplete nitric oxide and induce endothelial cell damage.[66,67] Clinical and observational trials of acute e-cigarette inhalation ± nicotine found significant increases in biomarkers of oxidative stress (n = 10–70).[43,45,48,50,61,62]

Overall, vaping acutely altered the human vasculature, likely as a result of sympathetic modulation and oxidative stress. While the long-term consequences of e-cigarette use on vascular health remain to be determined, there are reasonable grounds for concern that chronic vaping may impair vascular function in never-smokers. However, when compared to traditional cigarette smoking, some studies found that acute vaping caused less pronounced effects on vascular function and oxidative stress (n = 20–70).[45,48,61] Additionally, a recent large scale observational study (n = 2191 nonusers, 261 e-cigarette users, 3261 smokers, and 1417 dual users) found that both dual use and exclusive cigarette use were significantly associated with higher levels of inflammatory and oxidative stress biomarkers in blood, while exclusive e-cigarette use was not.[68] Further, a 2019 trial (n = 114) found that switching from traditional cigarettes to a first generation e-cigarette for one month led to a clinically significant improvement in FMD (1.49% [95% CI: 0.93 to 2.04%]) and a significant decrease in PWV (–0.53 [95% CI: –0.95 to –0.11]).[69] Overall, these findings suggest that from a vascular perspective, exclusive vaping has a profile of reduced harm when compared to cigarette smoking.

Associations Between Vaping and Pro-Thrombotic Biomarkers: To date, studies have indicated that vaping acutely induces platelet aggregation and activation.[45,47,63,70,71] These studies generally found that e-cigarettes have less pronounced effects on biomarkers of platelet activation and aggregation than traditional cigarettes.[45,70] Considering the importance of platelet activation in cardiovascular disease states including thrombosis, atherosclerosis, and myocardial infarction, the potential consequences of chronic e-cigarette use on this aspect of cardiovascular physiology requires further study.

Assessment of Myocardial Health in E-cigarette users: Over time, traditional cigarette smoking increases the risk of cardiovascular diseases including hypertension, atherosclerosis, and heart failure, suggesting that these outcomes should be monitored in chronic e-cigarette users.[51,52] Survey data showed that daily e-cigarette use was independently associated with higher odds of myocardial infarction (OR = 1.79 [95% CI: 1.20–2.66], n = 69,725).[25] While this study is limited by its cross-sectional design and requires longitudinal studies for validation, the findings underscore the importance of monitoring for secondary myocardial alterations that can occur following chronic pulmonary and vascular changes. To date, only one study has investigated the potential acute effects of e-cigarette use on myocardial function in adult smokers using echocardiography and reported no changes (n = 36).[72] However, acute/short term studies are not likely to induce cardiac remodeling, and thus are not a proxy for long-term studies. Critically, clinical trials and prospective studies investigating the effects of e-cigarette use on myocardial function have not yet been performed.

In summary, a shift in cardiac autonomic balance towards increased sympathetic drive,[73] increased oxidative stress,[74] increased vascular stiffness,[53] and endothelial dysfunction[75] all associate with increased cardiovascular morbidity and mortality. However, the evidence reviewed above regarding the cardiovascular effect of e-cigarettes is based on studies of small sample sizes, with limited clinical follow-up. Large scale studies designed to dissect the mechanisms by which e-cigarettes convey potential cardiovascular harm are needed to fully assess the safety of e-cigarettes. The current 2019 ACC/AHA guideline on primary prevention of cardiovascular disease recommend that clinicians ask all adults about e-cigarette use.[76] Critically, e-cigarettes are not recommended for tobacco cessation treatment.

E-cigarette Impact on the Respiratory System-Table 4—Pharmacokinetics have not yet been performed on e-cigarette constituents in the lung. However, it is estimated that nicotine levels are ~200 times higher in the lungs than at peak systemic levels after both smoking and vaping.[77] Chronic tobacco smoking damages the lung's ultrastructure and erodes innate immunity, leading to higher incidence of chronic obstructive pulmonary disease (COPD) and lung cancer. While it is not known whether vaping will produce lung disease, such signs (i.e. bronchitis, alveolar damage, decreased immunity to infection, wheeze etc.) are potential symptoms to be monitored in chronic e-cigarette users. Regarding lung function, differences between non-smokers and smokers are relatively small at young ages (i.e. 20–40 years) but become more significant over time (at 40–69 years of age).[78] Thus, care must be taken when interpreting lung function measurements following e-cigarette use, and the timeframes over which changes in lung function were captured must be factored into the analysis. Based on this review of the literature (Table 4), it appears that the majority of published clinical trials on e-cigarettes have not been of sufficient duration to detect significant differences in lung function between groups.

<u>**Effects of Vaping on Lung Function:**</u> Smoking cessation has been shown to halt the decline in lung function caused by combustible tobacco product use, but does not restore lung function.[79] Whether or not e-cigarette use is less harmful than conventional cigarette smoking is controversial (Table 4). Randomized clinical trials of acute and chronic e-cigarette use have shown variable results, with some showing reductions in lung function measured via spirometry[80,81], and others showing no change.[77,82–84] Using impulse oscillometry, which measures both small and large airway resistance and is more sensitive than standard spirometry, Vardavas et al. found elevated impedance in smokers after acute vape sessions (n = 30).[85] Due to the rapid timeframe, these changes were likely due to airway smooth muscle contraction (bronchoconstriction) rather than to lung damage.

In one study, there was no change in spirometry five days after switching from smoking to vaping of first generation e-cigarettes (n = 105).[86] Similarly, cigarette users who switched to vaping first generation e-cigarettes saw no improvement after 12 months (n = 183),[87] and in a randomized controlled trial where smokers were provided with either e-cigarettes or a nicotine-free cigarette substitute, no changes were detected between the two groups after 3 months (n = 263).[88] Unfortunately, these two studies did not include control groups who continued to smoke cigarettes. Collectively, switching from smoking to vaping did not

provide short-term benefits; however, longer trials with appropriate control arms are needed to determine if switching from smoking to vaping can improve lung function.

The above studies were all performed on healthy non-smokers or smokers. However, a number of individuals who have asthma, COPD, or other diseases also use e-cigarettes or switch from smoking to e-cigarettes.[89] While it is known that smoking cessation is beneficial and mitigates chronic declines in lung function,[90] a 24-month longitudinal study found that switching from smoking to vaping had no effect on spirometry in asthmatic smokers (n = 18).[91] Analysis of two observational cohorts (COPDGene, n = 3536; SPIROMICS, n = 1060) found that e-cigarette use was not associated with improved lung function in COPD patients, and instead showed higher prevalence of both chronic bronchitis and acute exacerbations.[92] This was a longitudinal study; however, it was observational in nature and more studies are needed to validate or refute this finding. Collectively, these data indicated that switching from smoking combustible tobacco to vaping does not improve lung function/respiratory health in patients with pre-existing lung conditions.

Assessment of Lung Damage in E-cigarette users: In a series of randomized clinical trials, an increase in the lung damage biomarker club cell protein-16 was detected in serum following acute exposure to e-cigarettes ± nicotine (n = 30, 25, 23).[46,93,94] Just 2 hours after e-cigarette exposure, 71 genes were significantly altered in airway biopsies and 27 genes were altered in primary alveolar macrophages, suggesting that vaping can elicit rapid responses in the lungs.[65] The effects of long-term vaping on pulmonary gene/protein expression remain understudied. However, proteomic analysis indicated that more proteins were uniquely changed in e-cigarette users' sputum (66) than in smokers' sputum (29), relative to healthy non-smokers (n = 15 e-cigarette users, 14 smokers, and 15 nonsmoker controls).[95] A number of innate defense proteins were altered.[95] Similarly, neutrophil elastase and matrix metalloproteases, which predispose lungs to damage, were equally elevated in smokers' and e-cigarette users' bronchoalveolar lavage (BAL) samples (n = 14 per group).[77] Proteomic analysis of bronchial epithelial brush biopsies identified uniquely altered proteins in e-cigarette users' lungs including mucins, calcium signaling-related proteins and xenobiotic metabolizing proteins (n = 10 e-cigarette users, 13 smokers, 18 nonuser controls).[84] These studies also found comparable increases in MUC5AC mucin levels in bronchial brush biopsies and sputum from both e-cigarette users and smokers relative to non-smokers.[84,95] Increases in expression levels of gel-forming mucins such as MUC5AC are predictive of COPD disease severity.[96] Interestingly, pulmonary function was normal across all groups,[84,95] which underscores the need for more sensitive assays beyond spirometry to assess lung function in healthy e-cigarette users. Lung imaging using computed tomography (CT) or other techniques may be useful in this regard but has not been tested in healthy e-cigarette users.

E-cigarette or Vaping product use-Associated Lung Injury: E-cigarette or Vaping product use-Associated Lung Injury (EVALI) is a point-source epidemic, multi-organ syndrome characterized by lung injury, gastrointestinal and other symptoms. CT scans of EVALI patients' lungs showed diffuse ground glass opacities, diffuse alveolar damage, interlobular septal thickening, and scarring of lower lobes, with sparing of the periphery.[97]

EVALI increased from a weekly mean of 4 visits per 1 million in January, 2017 to 116 visits per 1 million in autumn, 2019.[98] As of February 20, 2020, a total of 2,880 EVALI cases[99] and 68 EVALI-associated deaths were reported in the US;[100] current data collection has been ceased due to the COVID-19 pandemic; however, physicians should still inquire about tetrahydrocannabinol (THC) history in presenting patients. 82–86% of patients reported using THC-containing products while 14% used nicotine-based e-liquids but did not report THC use (n = 2,668).[99] One report found that vitamin E acetate was present in the BAL of 48/51 cases of EVALI across 16 US states[101]. Vitamin E acetate is commonly used as a thickening agent for THC vaping products and vitamin E acetate exposure induced inflammation and increased the number of lipid-laden macrophages in mice that was characteristic of EVALI.[102] These findings suggest that vape products containing vitamin E acetate are likely to be the causative agents of most EVALI symptoms and may also synergize with other harmful additives. Other harmful constituents found in e-liquids are trace metals such as Cd, Si, Cu, Ni, and Pb, although their contribution to EVALI remains uncertain they may pose as potential risks to e-cigarette users[103,104]. Due to challenges in diagnosis, the CDC approach for patients with suspected EVALI begins by examination of symptoms and assessment of e-cigarette or vape history and use within 90 days. THC history should also be assessed, but it is important to note that not all e-cigarette users may recognize this name and for some patients, slang names for THC should be tried (e.g. dab etc.).

Limitations and Future Directions

This review has several limitations. First, clinical trials examining the effects of vaping on cardiopulmonary health are heterogeneous and many were conducted over too short a timeframe to fully address the clinically important questions related to morbidity and mortality. Larger longitudinal studies with clinical follow-up will be crucial to determine the effects of e-cigarette use on cardiovascular health and inform guidelines for use of e-cigarettes as a smoking cessation tool. Second, studies assessing the effects of e-cigarettes on lung function were too short of a duration. Future longitudinal studies are needed to determine the effects of e-cigarette use on lung function and to assess whether lung function decline is halted when converting from conventional cigarettes to e-cigarettes. Third, the majority of studies enrolled adult smokers as opposed to younger e-cigarette users, who make up a sizeable majority of new users. Adult smokers have the potential confounder of pre-existing cardiovascular and pulmonary disease. Critically, the impact of vaping on adolescents and young adults requires further evaluation. Lastly, our search criteria were limited to English-language studies and may have not included relevant publications. In addition, knowledge gaps exist with a lack of prospective studies assessing the effects of e-cigarettes on clinical cardiovascular outcomes.

Conclusions

Observational epidemiological studies have associated vaping with higher incidence of pulmonary disease and myocardial infarction, and acute studies investigating pulmonary and cardiovascular biomarkers suggest tissue damage and compromised vascular function. Although these findings are largely limited to cross-sectional studies and short-term

clinical trials, current evidence of absolute harm signals that e-cigarettes could compromise cardiovascular and respiratory health over time. Several studies assessing relative harm suggest reduced harm for vaping compared to smoking; however, harm reduction has not been noted for all outcome measures studied (e.g. spirometry), and the extent of reduction in harm when smokers switch to electronic cigarettes is uncertain and requires further study. While e-cigarettes may facilitate smoking cessation, they are not associated with a reduction in nicotine use dependency and may lead to dual use of e-cigarettes and cigarettes. Clinicians should ask about and document e-cigarette use to enable the assessment of the health risks of e-cigarette use. Clinicians should also discourage nonsmokers and adolescents from using e-cigarettes and discourage smokers from engaging in dual use without cigarette reduction or cessation (Table 5).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Non-standard Abbreviations and Acronyms

e-cigarettes; EC	Electronic Cigarettes
TC	Tobacco Cigarettes
EVALI	E-cigarette or Vaping product use-Associated Lung Injury
NRTs	Nicotine Replacement Therapies
PWV	Pulse Wave Velocity
BAL	Bronchoalveolar Lavage
THC	Tetrahydrocannabinol

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Figure 1: First to Fourth Generation e-Cigarette Devices.
From left to right: first generation ("cig a-likes"), second generation ("vape pens"), third generation ("tanks" and "mods"), and fourth generation ("pod mods") e-cigarette devices. First and second generation e-cigarette devices were tubular and inefficient in nicotine delivery when compared to combustible tobacco products. Third generation devices were customizable and contained larger tanks with larger, higher voltage batteries and were comparable to conventional cigarettes in nicotine delivery efficiency. Fourth generation (e.g. JUUL, PuffBar) devices have smaller tanks (pods) and batteries with decreased nicotine delivery efficiency. However, fourth generation e-cigarettes compensated for lost efficiency by switching from freebase nicotine (used in first-third generation devices) to higher concentrations of nicotine salt, along with benzoic acid. These devices are available in reusable (left) and disposable (right) forms.
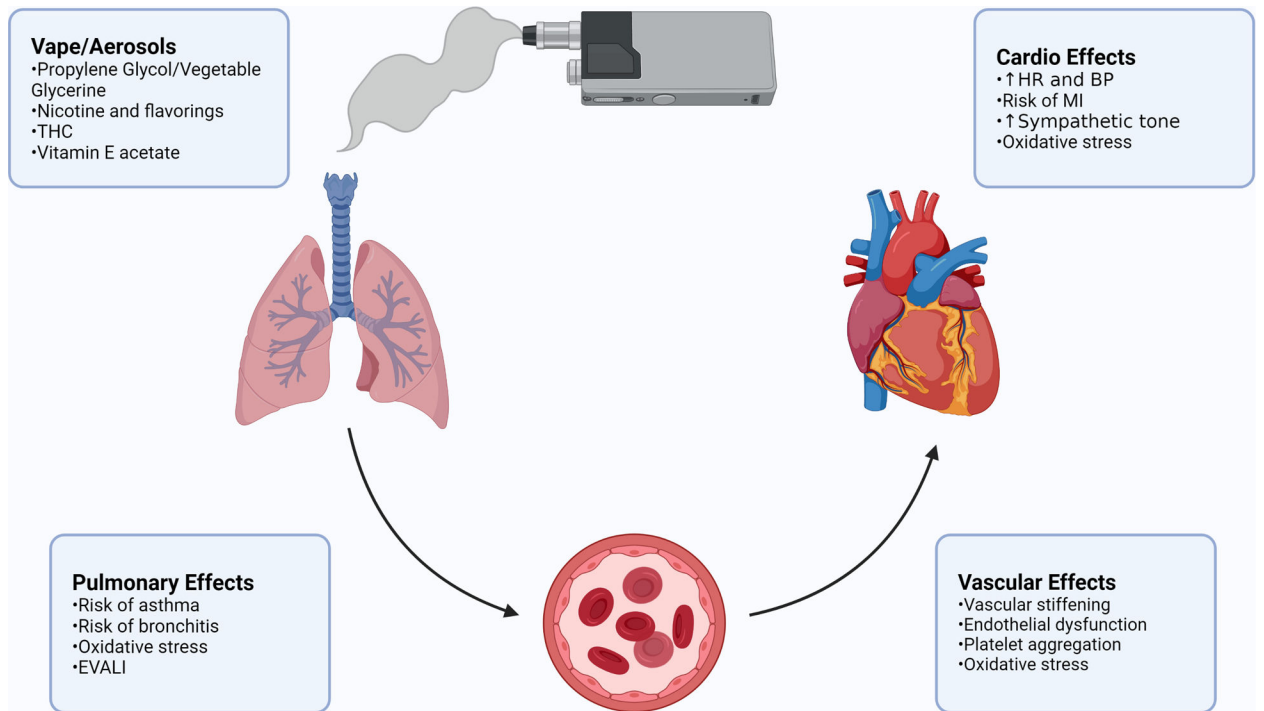
Figure 2. Overall Schematic.
Schematic representing the cardiopulmonary effects of various aerosols from e-cigarette vapor, and potential concerns for clinicians. Created with BioRender.com

Table 1:

E-cigarette Disease epidemiology

Design/Location, Year[ref]	Patient population, No.	Findings
Respiratory Symptoms and Disease		
Asthma		
Cross-sectional analysis/ South Korea, 2016[18]	N = 35,904 high school students	Prevalence rates of asthmatics was 3.9% in current e-cigarette users, 2.2% in 'former e-cigarette users', and 1.7% in 'never e-cigarette users'. The AOR for asthma for 'current e-cigarette' users was 3.41 (95% CI: 1.79–6.49).
Cross-Sectional analysis/US, 2019[19]	N = 402,822 never combustible cigarette smoker adults (> 18 years old) Current e-cigarette users, 3,103 (0.8%). 8.5% had asthma Median age group of current e-cigarette users was 18–24 years	Current e-cigarette use was associated with higher odds of self-reported asthma compared to never e-cigarette users (OR= 1.39; 95% CI: 1.15–1.68).
Chronic Bronchitis (chronic cough, phlegm, wheeze or bronchitis)		
Cross-sectional study/ California, US, 2017[20]	N = 2,086 youth (11th and 12th grade)	Risk of bronchitic symptoms was higher among past users (OR= 1.85; 95% CI: 1.37–2.49), and current users (OR= 2.02; 95% CI; 1.42–2.88), compared with never-users,
Cross-Sectional analysis/ Hawaii, US, 2019[21]	N = 8,087, mean age 55 years old	E-cigarette use was associated with chronic pulmonary disorder (AOR= 2.58; 95% CI 1.36–4.89, p<0.01).
Other respiratory symptoms		
Longitudinal analysis/US, 2020[22]	N = 46,000 ages 12 and older	Associations between former e-cigarette use (AOR= 1.31; 95% CI: 1.07–1.60) or current e-cigarette use (AOR= 1.29; 95% CI: 1.03–1.61) and respiratory disease. Current combustible tobacco smoking (AOR= 2.56; 95% CI: 1.92–3.41) was also associated with having respiratory disease.
Cross-sectional study/US, 2020[24]	N = 28,171 adults, 641 (1.2%) current exclusive e-cigarette users, 8525 (16.6%) were current exclusive smokers, 1106 (2.0%) were dual users, 17 899 (80.2%) were nonusers	Incidence of wheezing and related respiratory symptoms was higher in current e-cigarette users (AOR= 1.67; 95% CI: 1.23–2.15) compared with nonusers. Current e-cigarette users had lower risk of wheezing and related respiratory symptoms compared with current smokers (AOR= 0.68; 95% CI: 0.53–0.87).
Cardiovascular Disease		
Cross-sectional analysis/US, 2018[25]	N = 69,725 adults (>18 years)	Daily e-cigarette use was independently associated with higher odds of having had a myocardial infarction (OR= 1.79; 95% CI: 1.20–2.66, p=0.004) as was daily conventional cigarette smoking (OR= 2.72; 95% CI: 2.29–3.24).
Cross-sectional analysis/US, 2019[26]	N = 449,092 adults (>18 years)	No association between e-cigarette use and cardiovascular disease. Dual use was significantly associated with higher rates of cardiovascular disease vs smoking alone (OR = 1.35; 95% CI: 1.18–1.56).

Table Legend: OR = odds ratio, AOR = adjusted odds ratio, CI = confidence interval

Table 2:

Findings from e-cigarette Smoking Cessation Studies

Design, Location, Year[ref]	Sample Size/Patient Population	Device Generation	Findings
Meta-analysis, 2020[29]	50 studies representing 12,430 patients. 26/50 were randomized clinical trials.	N/A	Use of electronic cigarettes with nicotine improves smoking cessation rates compared to electronic cigarettes without nicotine (RR = 1.71 [95% CI: 1.00 to 2.92]) and nicotine replacement therapies (NRTs) (RR = 1.69 [95% CI: 1.25 to 2.27]).
Meta-analysis, 2021[37]	64 studies. 9/64 were randomized clinical trials.	N/A	In clinical trials, use of electronic cigarettes improves smoking cessation rates (OR = 1.529 [95% CI: 1.158 to 2.019]) compared to conventional therapies. However, observational study data showed that e-cigarette use as a consumer product was not associated with smoking cessation in adult smokers (OR = 0.947 [95% CI: 0.772 to 1.160]), nor in a subset of adult smokers who were motivated to quit smoking (OR = 0.851 [95% CI: 0.684 to 1.057]).
Meta-analysis, 2016[35]	20 studies representing 40,815 individuals. 2/20 were randomized clinical trials with 757 patients combined	N/A	The odds of quitting cigarettes were 28% lower (OR = 0.72 [95% CI: 0.57 to 0.91]) in those who used e-cigarettes compared to those who did not. This data was driven by observational studies, as the two clinical trials collectively showed no change in cessation rates.
Meta-analysis, 2017[34]	12 studies representing 14,122 individuals. 3/12 were randomized clinical trials with 1,007 patients combined	N/A	The odds of quitting cigarettes were 26% lower (OR = 0.74 [95% CI: 0.55 to 1.0]) in those who used e-cigarettes compared to those who did not. Results were of low certainty, however, based on the Grading of Recommendations Assessment, Development and Evaluation. approach
Randomized clinical trial, United Kingdom, 2019[31]	886 patients from stop-smoking services in the UK. Largely middle-aged smokers, median age 41.	2nd	1-year smoking abstinence rates were significantly higher (18%) for the e-cigarette group compared to 9.9% in the nicotine replacement therapy group (RR = 1.83 [95% CI: 1.30–2.58]). Patients in the e-cigarette group were more likely to still be using e-cigarettes (80%) than subjects who were treated with NRT (9%) after 1 year. 25% of participants in the e-cigarette group became dual users.
Randomized clinical trial, Canada, 2020[33]	376 patients with a moderate to strong desire to attempt to quit. Mean age 52.	2nd	12-week smoking abstinence rates were significantly higher for the nicotine e-cigarette group with counseling (21.9%) vs counseling alone (9.1%). Abstinence rates for the nicotine-free e-cigarette group with counseling were not significantly higher (17.3%) than counseling alone.
Randomized intervention trial, United States, 2018[36]	6,006 smokers employed by 54 US companies. Median age 44.	Unclear	6-month smoking abstinence rates were not significantly different in the e-cigarette group (1.0%) with standard care (free motivational text messaging and information about the benefits of cessation) versus the nicotine replacement therapy group (0.5%) with standard care nor standard care alone (0.1%).

Table 3:

Effects of e-cigarette use on the cardiovascular system

Acute EC Use, Clinical Trials						
Condition	**Biomarker**	**Change**	**Device Generation**	**Nicotine Concentration (mg/mL)**	**Flavor**	**Sample Size (n)**
Sympathetic Effects	HR	↑[42–47]	1st,2nd,3rd	0,1.5,3,18,24, Several, Unclear	None, Tobacco, Several	15,20,23,25,30
			44|45,47|42,43,46	43|46|43|47|42|44|45	43,46|42,45,47|44	42|45,47|44|43|46
		No Change[44,46,48]	1st,2nd,3rd	0,12,Several	None, Several, Unclear	23,30,70
			44|48|46	46,48|48|44	46|44|48	44|46|48
	Systolic BP	↑[42–46]	1st,2nd,3rd	0,1.5,3,24, Several, Unclear	None, Tobacco, Several	15,20,23,25,30
			44|45|42,43,46	43,46|46|43|42|44|45	43,46|42,45|44	42|45|44|43|46
		No Change[44,47, 48]	1st,2nd	0,12,18, Several	Tobacco, Several, Unclear	20,23,70
			44|47,48	48|48|47|44	47|44|48	47|44|48
	Diastolic BP	↑[43–45]	1st,2nd,3rd	0,3,Several, Unclear	None, Tobacco, Several	20,23,25
			44|45|43	43|43|44|45	43|45|44	45|44|43
		No Change[42,46–48]	2nd,3rd	0,12,18,24	None, Tobacco, Unclear	15,20,30,70
			47,48|42,46	46,48|48|47|42	46|42,47|48	42|47|46|48
	Tone	Sympathetic ↑[49]	2nd	12	Strawberry	33
		Vagal ↓[49]				
	HRV	↓[105]	1st (2nd hand exposure)	1.8	None	5
Vascular Stiffness	PWV	↑[42,43,48]	2nd,3rd	0,3,12,24	None, Tobacco, Unclear	15,25,70
			48|42,43	48|43|48|42	43|42|48	42|43|48
		No Change[43]	3rd	0	None	25
	AIx	↑[42,43,48]	2nd,3rd	0,3,12,24	None, Tobacco, Unclear	15,25,70
			48|42,43	48|43|48|42	43|42|48	42|43|48
		No Change[43]	3rd	0	None	25
Endothelial Function	NO Bioavailability	↑[45,61]	2nd,Unclear	Unclear[45,61]	Tobacco[45, 61]	20,40
			45|61			45|61
	FMD	↓[45,55,61]	1st,2nd, Unclear	0,Unclear	Tobacco, Unclear	20,31,40
			55|45|61	55|45,61	45,61|55	45|55|61
Endothelial Damage	EPCs	↑[64]	2nd	12	None	16
	Endothelial Microvesicles	↑[63]	3rd	19	None	17
		No Change[47,63, 64]	2nd,3rd	0, 12, 18	None, Tobacco	16,17,20
			47,64|63	63|64|47	63,64|47	64|64|47

Condition	Biomarker	Change				
Oxidative Stress	MPO	↑[43]	3rd	3	None	25
	MPO	No change[43]	3rd	0	None	25
	H2O2	↑[45]	2nd	Unclear	Tobacco	20
	sNOX2-dp	↑[45,61]	2nd, Unclear [45|61]	Unclear[45,61] [45|61]	Tobacco[45,61] [45|61]	20, 40 [45|61]
	8-iso-PGF2α	↑[45,61]	2nd, Unclear [45|61]	Unclear[45,61] [45|61]	Tobacco[45,61] [45|61]	20, 40 [45|61]
	MDA	↑[48]	2nd	0, 12	Unclear	70
	LDL-Ox, PON1, HOI	No Change[49]	2nd	12	Strawberry	33
Thrombotic Effects	Platelet Aggregation	↑[70]	Unclear	Unclear	Tobacco	40
	sP-selectin	↑[45,70]	2nd, Unclear [45|70]	Unclear[45,70] [45|70]	Tobacco[45,70] [45|70]	20, 40 [45|70]
	sCD-40L	↑[45,70]	2nd, Unclear [45|70]	Unclear[45,70] [45|70]	Tobacco[45,70] [45|70]	20, 40 [45|70]
	Platelet-derived Microvesicles	↑[47,63]	2nd, 3rd [47|63]	18, 19 [47|63]	None, Tobacco [63|47]	17, 20 [63|47]
		No Change[63]	3rd	0	None	17
Myocardial Effects	Systolic & Diastolic Function	No Change[72]	2nd	11	None	36

Observational Studies			
Condition	**Biomarker**	**Change**	**Subject Characteristics**
Sympathetic Effects	HR	No Change[58]	E-cigarette users (n =36), cigarette smokers(n =285), (both >4 days/week) vs nonuser controls (n =94)
	Systolic BP		
	Diastolic BP		
	Tone	Sympathetic↑[50]	Habitual e-cigarette users (n = 16) (>1year) vs nonuser controls (n = 18)
		Vagal ↓[50]	
Vascular Stiffness	PWV	No Change[58]	E-cigarette users (n =36), cigarette smokers(n =285), (both >4 days/week) vs nonuser controls (n =94)
	AIx	↑ *[58]	
Oxidative Stress	LDL-Ox	↑[50]	Habitual e-cigarette users (n = 16) (>1year) vs nonuser controls (n = 18)
	PON1	No Change[50]	
	HOI	No Change[50]	
	8-iso-PGF2α	No Change[68]	E-cigarette users (n = 261) vs nonuser controls (n = 2191)

Table Legend: HR = Heart Rate, BP = Blood Pressure, HRV = Heart Rate Variability, AIx = Augmentation Index, NO = Nitric Oxide, EPC = Endothelial Progenitor Cell, MPO = myeloperoxidase, sNOX2-dp = soluble NOX2-derived peptide, MDA = malondialdehyde, 8-iso-PGF2α = 8-iso-prostaglandin F2α, LDL-Ox = low-density lipoprotein oxidation, PON1 = paraoxonase 1, HOI = high-density lipoprotein antioxidant index, sP-selectin = soluble P-selectin, sCD-40L = soluble CD-40 ligand, 8-iso-PGF2α = urinary 8-isoprostane, hr = hour, d = day, wk = week

Vertical bars (|) separate references for each comma separated term in the respective box. Reference group for all studies were either baseline measures or within-subjects sham vaping/smoking control.

*= significant difference across groups via ANOVA, post-hoc of e-cigarette vs nonuser control not provided

Table 4:

Effects of e-cigarette use on the respiratory system

Design, year[ref]	Patient population	Device Type/Study Duration	Findings
Acute Studies Assessing Lung Function			
Double-blinded crossover study, 2019[106]	n = 17 occasional smokers, 6 males, mean age 26	3rd generation	Acute increase in flow resistance, indicating obstruction of the conducting airways.
Randomized Clinical Trial, 2018[94]	n = 23 occasional smokers, 16 males, mean age 23	3rd generation	Tissue hypoxia and lower airway injury.
Laboratory-based study, 2015[80]	n = 20 smokers (10) and nonsmokers (10), mean age 39	1st generation	No immediate adverse effects of nicotine-free vaping on non-smokers and only small effects on FEV1 and FEF25 in smokers.
Laboratory-based study, 2012[85]	n = 30 smokers, 14 men, mean age 35	1st generation	Increased respiratory impedance and resistance, likely indicative of airway bronchoconstriction.
Repeated-measures controlled study, 2013[107]	n = 30 smokers (15) and never-smokers (15), 16 males, age 18–57	2st generation	1-hour tobacco smoking, but not e-cigarette vaping transiently reduced lung function.
Crossover and placebo-controlled trial, 2017[82]	n = 20 (healthy, 20–37 years) and 10 (asthmatic, 21–40 years)	Unclear	1-hour vaping session of propylene glycol/glycerol did not significantly affect pulmonary functions in healthy or asthmatic subjects.
Acute Studies Assessing Lung Health Biomarkers and Omics Approaches			
Single-blind within-subjects study, 2019[93]	n = 25 smokers, 18 males, mean age 23	3rd generation	Increased biomarker of airway epithelial injury (serum CC16), sustained decrement in transcutaneous oxygen tension and impaired arterial oxygen tension.
Randomized, investigator-blinded, three-period crossover study, 2020[46]	n = 30 male e-cigarette users who were former smokers, mean age 38	3rd generation	Decreased lung inflammation, increased biomarker of airway epithelial injury (serum CC16), decreased transcutaneous O_2 tension.
Pilot clinical trial, 2020[108]	n = 30 never smokers, male and females, age 21–30	3rd generation; 4-week intervention period	E-cigarette use and inhalation correlated with change in cell counts (macrophages, and lymphocytes) and cytokines (IL-8, IL-13, and TNF-α). No significant changes in mRNA or miRNA gene expression.
Cohort Studies, 2018[65]	n = 10 adult never-smokers (21 years), 5 females	1st generation	Altered transcriptomes of small airway epithelium and alveolar macrophages for all subjects following inhalation of e-cigarette with nicotine.
Observational Studies			
Observational, cross-sectional study; sputum collection, 2018[95]	n = 44 adults (18 years); 14 current cigarette smokers, 15 current e-cigarette users, and 15 never-smokers	N/A	Increases in aldehyde-detoxification and oxidative stress-related proteins associated with cigarette smoke. Innate defense proteins associated with COPD, including MUC5AC, were elevated in e-cigarette users. Increases in neutrophil granulocyte-related and NET-related proteins.
Observational, cross-sectional study; research bronchoscopies, 2018[84], 2019[77]	n = 41–42 healthy, adults (>21 years), 19–20 female	N/A	Vaper airways appeared friable and erythematous. 113 uniquely altered proteins in e-cigarette users airways. MUC5AC elevated in e-cigarette users. Neutrophil elastase, MMP-2, and MMP-9 activities and protein levels were equally elevated in both e-cigarette users' and smokers' BAL relative to nonsmokers.
E-cigarette Assisted Cessation Trials			
Randomized controlled trial, 2019[88]	n = 263 smokers, 111 males, mean age 47	1st generation; 3-month cessation trial	No changes in standard spirometry.

Randomized controlled trial, 2017[86]	n = 105 smokers, 68 males, mean age 38	1st generation; 5 day cessation trial	No changes in standard spirometry.
Randomized controlled trial, 2016[87]	n = 130, 190 males, mean age 44	1st generation; 1 year cessation trial	No changes in most standard spirometry measures, improvement in $FEF_{25-75\%}$ among quitters.

Table Legend: CC16 = club cell protein-16, FEF25 = forced expiratory flow at 25%, IL = interleukin, TNF-α = tumor necrosis factor alpha, mRNA = messenger RNA, miRNA = microRNA, FeNO = fractional exhaled nitric oxide, eCO = exhaled carbon monoxide, MUC5AC = Mucin 5AC, NET = neutrophil extracellular trap, MMP = matrix metalloprotease, BAL = bronchoalveolar lavage

Table 5.

Considerations for Clinicians

• Clinicians should monitor patients not only for tobacco use, but also e-cigarette use and their associated health related problems.
• The use of e-cigarettes is associated with elevated cardiovascular risks and adverse impact on the lungs.
• The use of e-cigarettes is not safe for children, teens, young adults, and pregnant women, as well as adults not using traditional cigarettes.
• The long-term health effects of the use of e-cigarettes are not known.