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Publication Date

2020-10-01

DOI

10.1016/j.coi.2020.10.003

Peer reviewed

HHS Public Access

Author manuscript

Curr Opin Immunol. Author manuscript; available in PMC 2021 November 10.

Published in final edited form as:

Curr Opin Immunol. 2020 October ; 66: 143–150. doi:10.1016/j.coi.2020.10.003.

Vaping and e-cigarette use. Mysterious lung manifestations and an epidemic

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Abstract

Electronic (e)-cigarette use and the practice of vaping has rapidly expanded both in adult smokers and previously nicotine naïve youths. Research has focused on harm reduction in adults using e-cigarettes to stop or reduce traditional cigarette use, but the short and long-term safety of these products has not been established. Vaping has more recently been associated with a growing list of pulmonary complications with the most urgent being the e-cigarette or vaping product use-associated lung injury (EVALI) epidemic. This review details the inhalant toxicology of vaping products, the described lung diseases associated with vaping with a focus on EVALI, and the predicted long-term consequences of e-cigarette use, including increased asthma severity.

Keywords

E-cigarette; vaping; nicotine; toxicology; EVALI; acute lung injury (ALI); tetrahydrocannabinol (THC); Vitamin E acetate

Introduction

Electronic (e)-cigarettes are drug delivery devices primarily used for the inhalation of nicotine and marijuana, in the form of tetracannabinoids (THC). The modern e-cigarette was invented in 2003, entered the global market in 2007, and has rapidly become popular across the world. There are many types of e-cigarettes, from cig-a-likes to vape pens and box Mods to pod-devices, but they all involve heating and aerosolization of e-liquids (Figure 1). The

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Declaration of interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

base ingredients of e-liquids, nicotine, propylene glycol and glycerin, have an unappealing flavor on their own such that chemical flavorants are added to >99% of e-liquids to increase the appeal to users.

Use patterns of electronic (e)-cigarettes and vaping devices differ greatly across age groups. Adults most commonly pick up vaping in the setting of conventional cigarette smoking, either adding it into their smoking practice (dual use; 55% of adult e-cigarette users) or switching to e-cigarettes as a means to stop smoking[1]. While 3.2% of all adults use e-cigarettes, the rates are much higher in young adults 18-24 years-old, of whom 7.6% vape, and higher still in high school students, of whom 27.5% have used a vaping device within the past month[2,3]. Sadly, middle school students as young as age 11 also have high rates of e-cigarettes use (10.5%)[4]. While adult e-cigarette users are most often active smokers or ex-smokers, 44.3% of adolescents and young adults were never smokers prior to e-cigarette use[5]. Of concern, it has been shown that e-cigarette use in never smokers leads to higher initiation of cigarette smoking, up to four-fold[6-8]. A great deal of research to date has been focused on comparing e-cigarette use to cigarette smoking to assess the potential benefit of switching from smoking to vaping as a form of harm reduction, while less focus has been on the health effects of vaping in non-smokers, for whom the rates of vaping continue to rise, particularly in the youth[9,10].

E-cigarettes have been marketed as a form of harm reduction from traditional cigarette smoking, but neither the safety nor the efficacy of these devices has been established, and little is known about the short and long term pulmonary and systemic health effects. This review focuses on the known and unknown toxins contained in e-cigarette aerosols, lung diseases induced by vaping, and the predicted long-term consequences of e-cigarette use. Particular attention is given to the e-cigarette or vaping product use-associated lung injury (EVALI) epidemic that began in 2019 and is ongoing.

Inhalant Toxicology of E-cigarettes and Vaping Products

E-cigarettes are devices composed of a power source, heating element, and liquid reservoir that heat and aerosolize e-liquids to make vapor that is inhaled into the lungs in a process known as vaping. E-liquids are most often composed of 1) Addictive substances such as nicotine and/or tetrahydrocannabinol (THC), 2) Flavorings, and 3) Solvents (e.g., propylene glycol or vegetable glycerin). There are many types of vaping devices, but the most frequently used include pod vapes, box mods, and vape pens (Figure 1). The pod devices were widely popularized by the company Juul, which developed its sleek device to look like a flash-drive that quickly became the most profitable e-cigarette by the end of 2017[11]. The e-liquids in Juul pods contain high concentrations of the more rapidly absorbed nicotinic salts complexed with benzoic acid, compared to free based nicotine, thus increasing the addictive potential and toxicity[12]. Given that nicotine exposure influences long-term molecular, biochemical, and functional changes in the adolescent brain, it is not surprising that teens who vape are at increased risk of subsequent use of traditional cigarettes, marijuana, opioids, and other illicit drugs with addictive potential[13-15]. THC also induces alterations in reward networks in the adolescent brain, which increases risk for future drug

use, and regular cannabis users of any age have poorer neurocognitive functioning and functional brain alterations relative to nonusers[16,17].

Although vaping devices are not an approved nicotine replacement therapy, the Federal Drug Administration (FDA) has allowed e-cigarette manufacturers to design e-liquids using components that have been ”generally recognized as safe” (GRAS). Compounds that have GRAS status are only assessed as safe to ingest via the gastrointestinal (GI) tract, or put on the skin. Thus, the vast majority of compounds with this designation have not been tested for safety via the inhalation route. There are thousands of different flavoring ingredients used, and thermal decomposition of propylene glycol, glycerol, and flavoring agents result in the production of toxic aldehydes at levels that exceed occupational safety standards[18,19]. Chemical flavorings such as diacetyl and 2,3-pentanedione, present in many e-liquids, have been found to induce transcriptomic changes that disrupt cilia function in human airway epithelium, impairing mucociliary clearance [19,20]. Cumulative exposure to diacetyl is well known to be associated with the development of the irreversible airway fibrosing disorder bronchiolitis obliterans (BO), with the term “popcorn lung” used when referring to BO described in microwave popcorn factory workers [21,22]. Other toxins found in e-cigarette vapor with inhalant and systemic toxicities including terpenes, acrylonitrile, formaldehyde, crotonaldehyde, propylene oxide, acrylamide, and heavy metals [23,24]. None of these products are currently regulated, but there is even greater cause for concern regarding the inhalant toxicity for the components in “black market” or counterfeit e-liquids and devices as well modified devices. Finally, microbial toxins may contaminate vaping devices even prior to use. One study tested the leading U.S. pod vape and found that 81% of devices contained B-D-glucan, a fungal cell wall marker, and 23% contained endotoxin, found in the outer wall of gram-negative bacteria[25]. Both of these microbial contaminants are associated with asthma and hypersensitivity pneumonitis [26,27].

Currently Known Pulmonary Manifestations of Vaping

E-cigarettes have been marketed as a form of harm reduction from traditional cigarette smoking, but neither the safety nor the efficacy of these devices has been established, and little is known about the short and long term pulmonary and systemic health effects. There have been increasing reports in the literature of negative pulmonary effects with the recent epidemic of e-cigarette or vaping product use-associated lung injury (EVALI) (discussed in detail below) being the most immediately concerning. Reports of the development of chronic respiratory symptoms, increased asthma morbidity, and the development of diffuse lung disease in both adolescents and adults highlight significant pulmonary toxicity and compel further research.

E-cigarette users are more likely to report chronic respiratory symptoms and conditions in both adolescents and adults. In a large study from Hong Kong of 45,000 adolescents who vaped in the previous month reported chronic cough or phlegm production with increased odds[28]. In a smaller study of 2,000 high school students in Southern California, past and current vaping was associated with a nearly two-fold increase in the risk of chronic bronchitis symptoms[29]. In a longitudinal analysis of adults in the Population Assessment of Tobacco and Health (PATH) Waves 1, 2, and 3 with data collected from 2013-2016, a

significant association between former and current use at Wave 1 and incident respiratory disease at Waves 2 or 3 was demonstrated, controlling for combustible tobacco smoking and other demographic, and clinical variables. In this study, dual use of cigarettes and e-cigarettes had increased odds of developing respiratory disease of 3.30 compared with a never smoker/vaper[30].

Among asthmatic patients, primary e-cigarette use and secondhand exposure confers increased morbidity. Interestingly, vaping is more popular among asthmatic teenagers as compared to their non-asthmatic peers[31]. The reason for this observation is unclear, but may be related to the commonly held belief that vaping is safer than smoking cigarettes. Among adult never cigarette smokers, current e-cigarette use was associated with 39% higher odds of self-reported asthma compared to never e-cigarette users[32]. In South Korea, vaping in high school students was associated with increased odds of being diagnosed with asthma and more missed days of school secondary to asthma[33]. The Florida Youth Tobacco Survey showed that past-30-day e-cigarette use was associated with having an asthma attack in the past 12 months among high school participants with asthma[34]. This survey later revealed that 33% of 11- to 17-year-olds with asthma had secondhand e-cigarette exposure, and this exposure was associated with increased risk of asthma exacerbation[35]. There are also case reports of two adolescent asthmatic e-cigarette users who presented with life-threatening status asthmaticus requiring VV-ECMO[36]. This may indicate increased risk for more severe exacerbations among asthmatic teens who are vaping. In addition, EVALI cases from both the Illinois and Wisconsin cohort and Rochester cohort reported higher- than expected rate of EVALI in asthmatics[37,38].

Vaping has been linked to various rare pulmonary conditions and pathologic abnormalities. There have been multiple case reports of different types of severe and life-threatening diffuse lung disease in patients using vaping products including hypersensitivity pneumonitis, eosinophilic pneumonitis, diffuse alveolar hemorrhage, lipoid pneumonia and bronchiolitis[39,40,41-52,53]. These case reports demonstrate that there is undeniable harm associated with vaping even before decades of use. Among patients with EVALI, pathology results included findings consistent with acute lung injury including acute fibrinous pneumonitis, diffuse alveolar damage, and organizing pneumonia[54,55]. Taken together these pathological findings indicate that severe lung injury in multiple different patterns can occur in the setting of vaping. Although the mechanism of injury in these patients is currently unknown, it is presumed that there are both product and host related factors contributing to lung injury[56]. Given that multiple components of vaping products can cause pulmonary toxicity, it is unlikely that there is only one chemical component leading to these diverse patterns of toxic lung injury. Beyond the scope of this review are systemic toxicities as well as trauma due to explosions, thermal injuries and acute intoxications including ingestion of e-liquids[57,58].

EVALI

The national outbreak of e-cigarette, or vaping, product use-associated lung injury (EVALI) has been the first vaping related disease to affect thousands of people (2,807 hospitalized cases as of February 2020). At its core, it is a chemical inhalation injury, most likely caused

by heating, aerosolization and inhalation of Vitamin E within THC liquids and vape pens. Examination of airways and lungs of those affected has yielded a pattern of epithelial and alveolar damage[55]. Neutrophils and foamy macrophages are often documented, with lipid laden phagosomes when directly tested through appropriate lipid stains[54,59]; however, lipid laden macrophages are most likely evidence of vaping in general, not specific to EVALI[60]. Although it has been clear for years that users of e-cigarettes and vaping devices were inhaling known toxins such as diacetyl and formaldehyde, this disease entity was the first to demonstrate that inhalation of clouds of chemicals that have never been tested for safety via inhalation methods can lead to significant impacts on public health.

EVALI was first recognized in August 2019, with the number of recognized cases rising precipitously until December 2019[61]. The connection with THC was made within several weeks – approximately 82% of those affected had vaped THC (https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html#latest-information) – while the identification of Vitamin E acetate as a prime suspect took months, and has not been confirmed as the etiologic agent at this time (April 2020)[62,63,64]. Fourteen percent of those affected vaped nicotine containing e-liquids only, but upon review these subjects were older, female and had less leukocytosis, suggesting that they may have been suffering from a different vaping induced lung disease[65].

Overall, EVALI is a disease of the young, with a median age of 24 years. It also predominantly affects males (66%), which may be directly related to epidemiologic patterns of THC vaping. The majority of patients present with respiratory (cough and/or shortness of breath), gastrointestinal (nausea, diarrhea, and/or abdominal pain) and systemic (fever) symptoms, and are found to have elevations in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), white blood cell counts, and liver function tests. Beyond these factors, bilateral lung infiltrates are the key diagnostic finding on radiographic imaging.

The mortality rate is quite low, at 2.4% (68 total deaths), with the highest mortality rate in older e-cigarette users with comorbidities. The median age of deceased EVALI patients was 49.5 years, with a range from 15 up to 75 years. Of the cases identified up to December, approximately 47% required ICU admission and 22% required intubation[66]. Because only moderate to severe cases were tracked, the reported numbers are likely to severely underestimate those affected. Since Vitamin E acetate (VEA) within THC e-liquids has been identified as a likely causal agent, and with the intense media coverage of this disease entity, there is hope that the incidence of this particular vaping disease will decrease. However, as vaping increases across society, with millions of users inhaling hundreds of thousands of chemicals including lipophilic agents similar to VEA, it is clear that vaping associated lung diseases are here to stay.

Predicted long-term health consequences

Conventional tobacco has been smoked for over 5000 years and is very well known to cause a myriad of long-term health problems, not the least of which is lung disease[67]. Because modern vaping devices have been on the market for less than 16 years, and only widely used for 5, very little is known about how chronic use will affect human health. Murine data

suggest that some vapers will develop emphysema, heart disease, renal failure, and even liver fibrosis, but these diseases will be couched in genetic predisposition, type of e-device used and the chemicals within the inhaled aerosol[57,68,69]. Because vaping aerosols contain chemicals that cytotoxic and cause DNA damage, it is unsurprising that murine models have demonstrated increased occurrence of lung toxicities [70,71]. Thus, it is hypothesized that long-term vaping will lead to increased incidence of cancer.

Less is understood about the long-term effects of vaping on asthma. Because acute and sub-acute vaping can increase airway resistance and airway reactivity, it is believed that chronic use of e-cigarettes will lead to more severe disease in asthmatics[9]. Vaping alters the function of myeloid cells, including granulocytes, such that it is likely that vaping will alter the function of eosinophils as well, leading to vaping induced changes in allergic diseases[58,72]. Asthma has many phenotypes, including eosinophilic and neutrophilic sub-types, and with the knowledge that vaping has broad effects on immune cells, e-cigarette use may impact multiple asthma phenotypes [73].

Studies in humans thus far are limited to acute and short-term effects, but consistently demonstrate that vaping impacts both pulmonary and cardiovascular function[9]. Gene expression from airway samples evidence changes that parallel those in cigarette smoking, which is worrisome in that it predicts that vapers will develop the same lung diseases that smokers do – namely emphysema, chronic obstructive pulmonary disease (COPD), and respiratory bronchiolitis interstitial lung disease (RB-ILD)[74-76]. In addition, altered human neutrophil function suggests that vapers will be at higher risk for bacterial infections as well as autoimmune disease[77,78]. While longitudinal studies on the health effects of chronic e-cigarette use are needed, the data thus far suggest that vaping will have substantial adverse impacts across organ systems, leading to significant morbidity and mortality over time.

Conclusions

Vaping involves the introduction of hundreds to thousands of chemicals into the delicate airways and alveoli of the lung, causing a myriad of both acute and chronic diseases in humans. Some diseases such as EVALI, HSP and acute eosinophilic pneumonia are already recognized, but as more and more people begin vaping and vape for longer periods of time, more diseases both in the lung and throughout the body will become apparent. Prevention of these known and unknown effects of vaping is a priority to the field of pulmonary medicine, and advocacy for flavor, device, and nicotine level restrictions at the national level to prevent further use by children and young adults is extremely important. Further research to define the effects of vaping on pulmonary, cardiac, mental, and systemic health is desperately needed.

Acknowledgments

Funding: Dr. Crotty Alexander's salary was supported in part by the VA San Diego Healthcare System and grants from the National Institutes of Health (NIH R01HL147326 to LCA) and the Tobacco-Related Disease Research Program (TRDRP T30IP0965 to LCA and 26IP-0040 to LCA).

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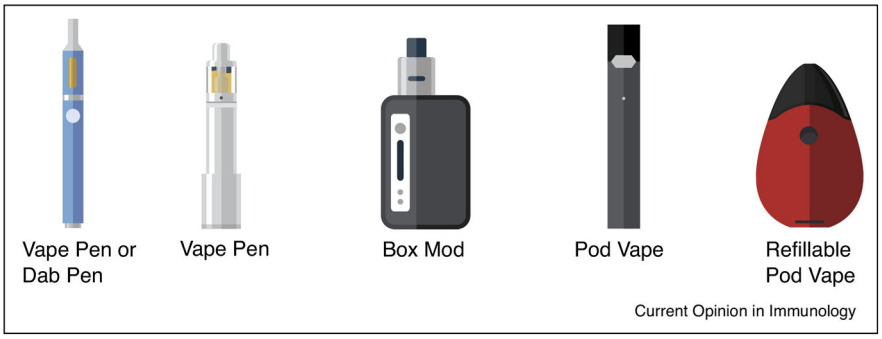

Figure 1.

E-cigarette devices have evolved rapidly over the 13 years they have been on the international market. Vape pens, box Mods and pod devices are all currently popular. Each of these vape devices heat and aerosolize e-liquids that contain nicotine or THC.

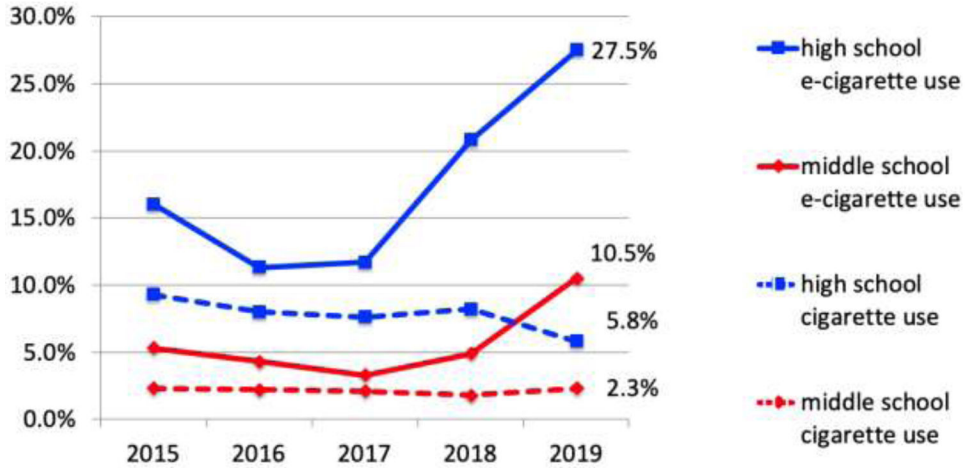

Figure 2.

NYTS data from 2015-2019 demonstrating the dramatic increase in e-cigarette or vaping device use in high school and middle school populations, which is believed to be driven primarily by the popularity of the pod-based vape JUUL. *Centers for Disease Control and Prevention National Youth Tobacco Survey (NYTS); 2019*.

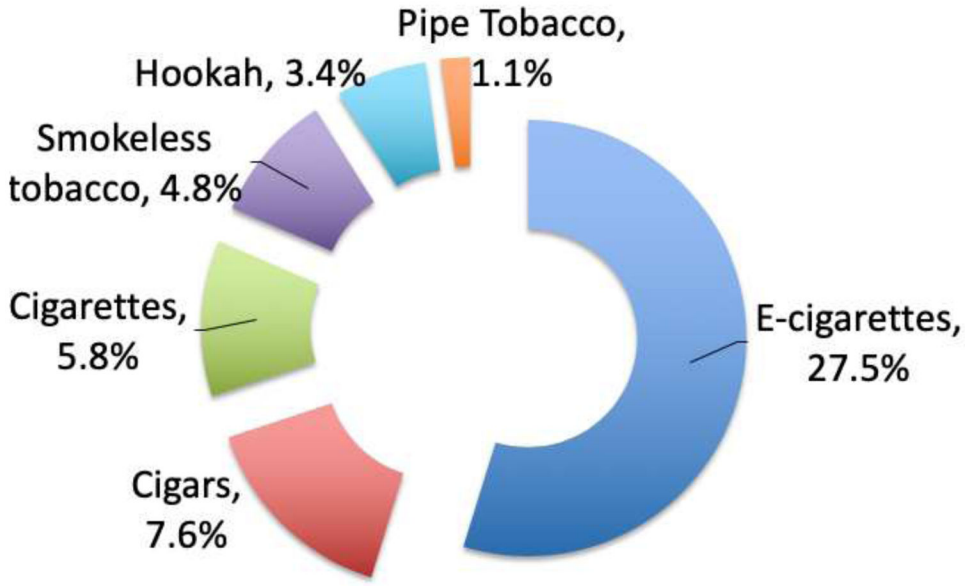

Figure 3.

Breakdown of conventional tobacco and e-cigarette / vaping product use in the 4.7 million high school students who report tobacco use from the NYTS 2019 data. *Centers for Disease Control and Prevention National Youth Tobacco Survey (NYTS); 2019*.

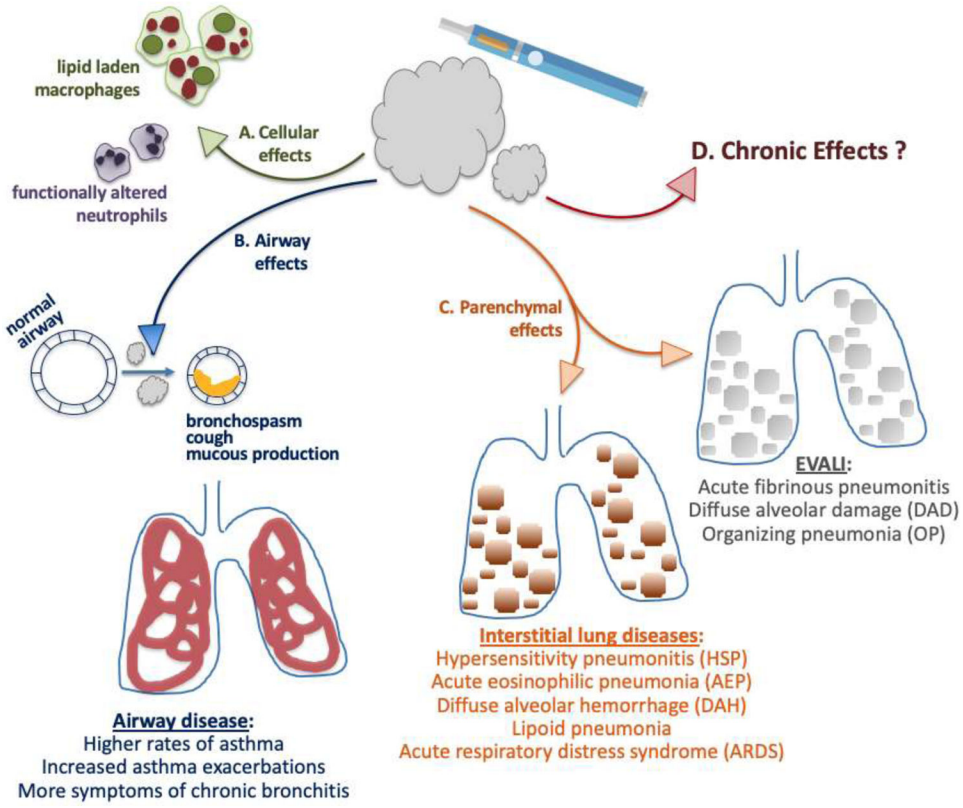

Figure 4.

A. Exposure to e-cigarette aerosols alters innate immune cells both in the lungs and in the circulation. **B.** Vaping causes bronchospasm and mucous production leading to the development of respiratory symptoms (cough and shortness of breath) associated with chronic bronchitis. Vaping also leads to increased odds of being diagnosed with asthma and more missed days of school secondary to asthma, increased asthma exacerbations and attacks, and more severe asthma attacks. **C.** Vaping has been associated with the development of diffuse lung diseases in both adolescents and adults over the last ten years. In 2019, vaping was found to cause the disease known as EVALI, with associated pathologic patterns of acute fibrinous pneumonitis, diffuse alveolar damage, and organizing pneumonia found by lung histopathology. **D.** Based on the in vitro, in vivo and human subjects research completed to date, chronic inhalation of e-cigarette aerosols will lead to pathologic changes in the lungs and lung disease.