Electronic Cigarettes and Vaping in Allergic and Asthmatic Disease

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KEYWORDS

• E-cig • Electronic nicotine delivery systems • ENDS • Vaping
• E-cig or vaping-associated lung injury • EVALI • Smoking cessation

KEY POINTS

- Vaping has become popular in many high-risk patient populations, including asthmatics and youth, both as an initial choice and an alternative to combustible cigarettes.
- The liquid used in vaping may cause adverse effects such as alterations in epithelial and sputum proteomes, airway gene expression, and mucus composition.
- E-cigarette (e-cig) or vaping product use-associated lung injury (EVALI) is a rare potentially severe and life-threatening acute or subacute illness often linked to vitamin E acetate.
- More information is needed about the long-term risks of vaping, specifically in high-risk patient populations like those who suffer from asthma and allergies.

INTRODUCTION

Electronic nicotine delivery systems (ENDS) such as e-cigarettes (e-cigs), vape pens, e-hookahs, e-pipes, tanks, mods, vapes, and other systems were introduced in 2006, offering alternatives to combustible cigarettes.[1,2] Their popularity is increasing due to stricter guidance on public smoking, advertising, discretion, and perception of a safer alternative to combustible cigarettes. There is significant controversy regarding their sale and regulation, particularly with youth. While also used for smoking cessation,[3] e-cigs have been cited as a gateway to drug use and subsequent use of combustible cigarettes.[4] They were deemed a "major public health concern" by the United States (US) Surgeon General in 2016.[5] Already associated with health consequences, recently e-cig or vaping product use-associated lung injury (EVALI) has exposed their potential to cause life-threatening complications.

This publication aims to educate readers on immediate and long-term health consequences of ENDS, so they may provide patient counseling on utilization focusing on the asthmatic population.

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SALES AND UTILIZATION

ENDS cornered the market by using product placement and reemploying advertising strategies used for traditional cigarettes banned in 1971.[6] Sales spiked from $6.4 million in 2011 to $2 billion in 2018.[5,7] Devices are relatively inexpensive and readily available.[1] With their small, discrete shape and lack of large vapor cloud, products such as JUUL are popular with youth and young adults, dominating the US market with nearly 70% of the sales.[8] "JUULing" has become a verb in popular culture. E-cig use surpassed traditional cigarettes in US youth in 2014.[5] Recent data on utilization:

- 4.2% of the surveyed adults currently using e-cigs were dual users.[5]
- 10.9% of surveyed US college students vaped tetrahydrocannabinol (THC) in 2018, up from 5.2% in 2017.[9]
- Estimated 5 million (27.8%) US high school students surveyed in 2019 used e-cigs, up from 20.8% in 2018% and 1.5% in 2011.[10,11]
- 11% of seventh grade students used e-cigs versus 6.8% used combustible cigarettes, and 42.2% had also used combustible cigarettes.[5]

Data from the National Youth Tobacco Survey revealed the common reasons youth began using ENDS (**Table 1**). One report found that 63% of surveyed JUUL users did not know that JUUL products always contain nicotine.[12] Evidence current e-cig users will evolve into dual users is mounting.[11]

Utilization in asthmatics is alarming, increasing from 20.3% (2014) to 29.1% (2017), most noticeable in those aged 18 to 24.[13] E-cig utilization may be more prevalent in asthmatic teens versus nonasthmatics as they report feeling less likely to become addicted and e-cigs were less harmful than cigarettes.[14–19]

Unfortunately, the data on increased utilization coupled with potentially at-risk populations highlights need to improve regulations, utilization screening, and patient counseling.

FEDERAL REGULATION AND WARNINGS

The Food and Drug Administration (FDA) Center for Tobacco Products regulates the manufacturing, importing, packaging, labeling, advertising, promotion, sale, and distribution of ENDS but does not have the ability to regular accessories. As of 2019, purchasers must be 21 by federal law.[20,21] Although often used for smoking cessation, they have not been approved by the FDA for this purpose due to lack of long-term use data and potential risk of EVALI and other potential serious lung disorders.[1]

DELIVERY DEVICES

Delivery systems include closed or open systems and tank or pod mods (**Fig. 1**). Open systems hold refillable e-liquid reservoirs enabling customization. Favored by youth with their discreet size and small vapor cloud, closed systems are concealable. Products are comprised of a mouthpiece, atomizer producing the aerosol from the liquid, battery (commonly rechargeable lithium), and sensor (**Fig. 2**). Powered e-cigs (brands:

Table 1
Reasons youth began using ENDS

Use by a Family or Friend	39%
Availability of flavors	31%
Belief they are less harmful than other forms of tobacco (cigarettes)	17.1%

Fig. 1. Vaping product classification. (*From* E-cigarette, or Vaping, Products Visual Dictionary. Centers for Disease Control. Accessed April 28, 2022.https://www.cdc.gov/tobacco/basic_information/e-cigarettes/pdfs/ecigarette-or-vaping-products-visual-dictionary-508.pdf.)

JUUL, Bo, and myblu, and so forth) resemble USB devices, whereas disposables (brands: Zig Zag, Vapor4Life, V2, White Cloud, and so forth) are shaped like traditional cigarettes.[1] Vape peds (JUUL, Aspire, Apollo, Kanger, and so forth) feature discrete medium tanks.[1]

Tank mods have a customizable temperature, wattage, and nicotine (0–36 mg) delivery settings through their electronic control box (tank) along with refillable reservoirs. They are favored for smoking cessation to allow reducing nicotine exposure. Tank systems (brands: Aspire, Smok, Vaporesso, Kangertech, and so forth) may be disposable or rebuildable.[1]

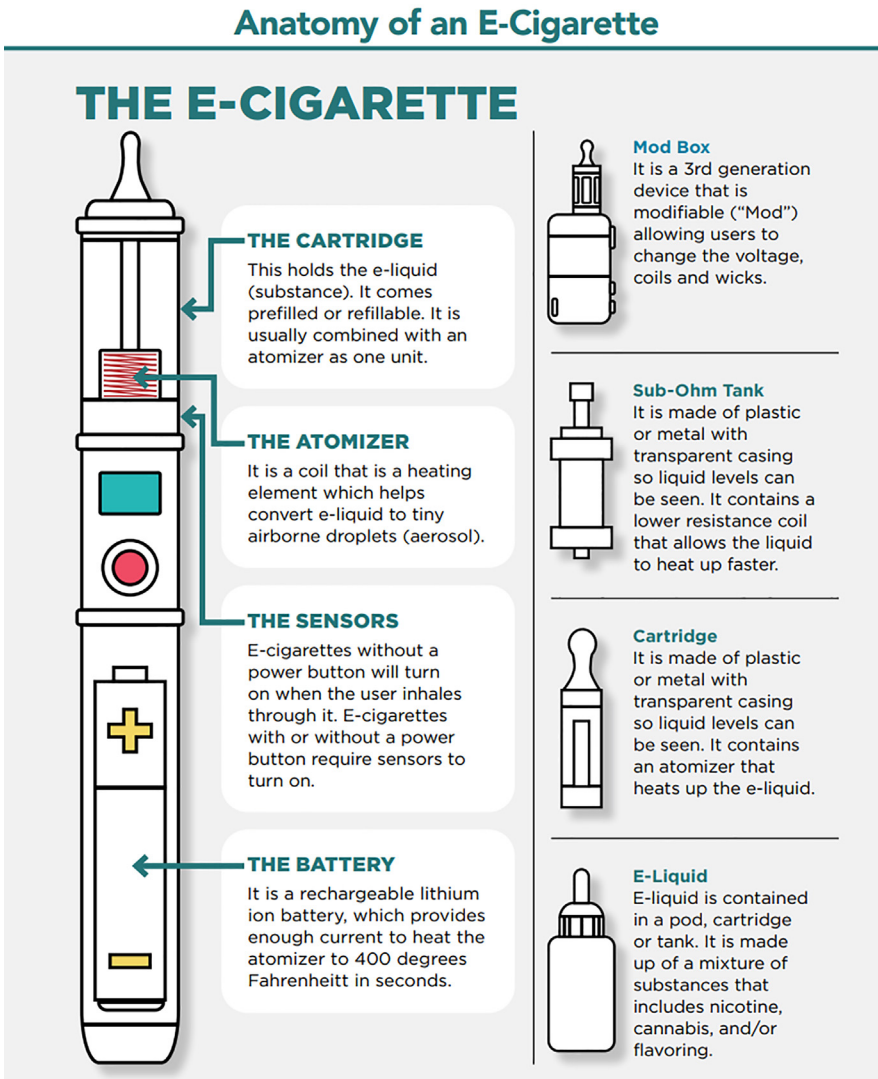

Fig. 2. Anatomy of a vape pen. (*From* E-cigarette, or Vaping, Products Visual Dictionary. Centers for Disease Control. Accessed April 28, 2022.https://www.cdc.gov/tobacco/basic_information/e-cigarettes/pdfs/ecigarette-or-vaping-products-visual-dictionary-508.pdf.)

Pod mods such as JUUL are inexpensive and feature discrete designs popular with youth and young adults. These products can deliver large amounts of nicotine disguised by flavorings unregulated by the FDA that have been proven to entice youth to begin experimentation with utilization.[12,22,23]

E-LIQUIDS

E-liquids and e-juices are flavor-filled inhalable aerosols that disguise the nicotine.[1] They contain flavoring, a solvent (vegetable oil/glycerin [VG] or propylene glycol [PG]), and varying quantities of nicotine. They turn into vapor by the heating element

activated by a switch when the user inhales via the mouthpiece and the sensor detects a change in airflow, causing the battery to activate the atomizer to aerosolize the liquid. Depending on the product, a variety of chemicals may be found in the aerosols, many of which may be at toxic levels (**Box 1**).[8,24–27] Devices may also be used for vaping other products including THC, synthetic cannabinoid receptor agonists, crack cocaine, lysergic acid diethylamide (LSD), and methamphetamine.[28]

NICOTINE

Nicotine, a natural alkaloid component found at the highest concentrations in the leaves of the tobacco plant (*Nicotiana tabacum*), is a highly addictive stimulant.[29] Heating to decomposition emits nitrogen oxides, carbon monoxide, and highly toxic fumes.[30] Pharmacokinetics depend on the rate, location, and extent of absorption (**Table 2**). Nicotine is renally excreted (half-life of 1–3 hours) with more than 20 metabolites. While not pharmacologically active in humans, cotinine has a plasma half-life of 10 to 40 hours and may be used to assess for nicotine use in blood, hair, and urine.[31] The reported fatal adult dose is 40 to 60 mg or less than 5 mg/kg.[32,33] The nicotine delivery with ENDS varies between 3 and 36 mg/mL ranging up to 80 mg/mL.

Nicotine is an agonist of the nicotinic acetylcholine receptors, including those expressed in airways inhibiting cystic fibrosis transmembrane conductance regulator (CFRT) in airway epithelia.[29,34] It causes oropharyngeal mucosal inflammation, ulceration, altered taste, and skin irritation when applied topically. Dopamine release and binding of its receptors gives way to nicotine-induced euphoria and addiction.[31] Toxic effects include cardiac arrhythmia, vasoconstriction, hypertension, hyperglycemia, nausea/vomiting, abdominal pain, diarrhea, confusion, weakness, increased salivation and lacrimation, and respiratory alteration.[29,31] When delivered in a lower pH salt form, nicotine absorption is enhanced, and becomes less irritating.[35,36]

Tolerance and physical dependence may occur when smoking more than 100 to 150 mg of nicotine per day. Withdrawal symptoms vary, usually appearing within 24 hours of abstinence, and are characterized by behavioral changes, headache, and drowsiness.[31] Smoking while pregnant has been associated with increased risk of spontaneous abortion, low birth weight, and still birth.[32] Nicotine has been found to be a cocarcinogen in animals.[32]

FLAVORING ADDITIVES

There are greater than 7000 e-cig flavors including tobacco, menthol, fruit, candy, soda, and alcohol flavors commonly formed by ethyl maltol, ethyl vanillin, vanillin,

Box 1
Vaping aerosol contents

Organic Volatile Compounds: Propylene Glycol, Toluene, Glycerin

Aldehydes: formaldehyde, acetaldehyde, benzaldehyde

Acetone

Acrolein

Carcinogenic nitrosamines

Polycyclic aromatic hydrocarbons

Particulate matter

Metals: Chromium, cadmium, nickel, lead, copper, silver

Table 2
Nicotine absorption

Product	Time to Peak Concentration
Intranasal spray	4–15 min
Chewing gum	25–30 min
Oral inhalation	15–30 min
Transdermal	2–10 h

cinnamaldehyde, and menthol. While typically considered safe for oral ingestion, there is limited evidence suggesting they are not safe when inhaled. In 2012, the Flavor and Extract Manufacturers Association of the United States identified priority flavoring agents with potential adverse lung effects including acetaldehyde, acetoin, benzaldehyde, diacetyl, cinnamaldehyde, and ethyl acetate.[37]

Flavoring agents can create toxic transformation products with aerosolization and heating. Aldehyde/formaldehyde and benzene formation, known carcinogens, occur primarily due to the aerosolization of flavoring compounds.[38,39] In vitro exposure to flavoring used in ENDS can be cytotoxic to human monocytes and has been found to trigger inflammation and oxidative stress.[40] Aromatic aldehydes (ie, cinnamaldehyde, benzaldehyde, and vanillin) impair neutrophil function.[41] Cinnamaldehyde caused a dose-dependent impairment in mitochondrial respiration and glycolysis, temporary reduction in adenosine triphosphate levels in human bronchial epithelial cells, and rapidly transiently suppressed ciliary beat frequency.[42]

PROPYLENE GLYCOL AND VEGETABLE GLYCERIN

In vitro and in vivo models demonstrate adverse changes in the airway due to PG and VG including airway remodeling, elevated MUC5AC in epithelial cell cultures, reduced membrane fluidity, and impaired protein diffusion.[43] PG and VG adversely airway epithelial cell viability.[44]

A pilot study of never smokers who underwent serial bronchoscopies after only PG and VG exposure revealed changes in BAL inflammatory cell counts and proinflammatory cytokines.[45] Contrary to their advertised inert biological behavior PG and VG may account for a significant portion of the airway damage in ENDS users.

PULMONARY COMPLICATIONS

Evidence is emerging on the detrimental health effects of ENDS, some resembling combustibles. ENDS devices use a variety of delivery systems, nicotine content, flavoring, and liquid compounds which can be customized, some products may be more detrimental than others.

In vitro airway models exposed to nicotine reveal macrophage activation[35] and impaired mucociliary clearance with altered epithelial cell surface liquid, mucous concentration, and mucous viscosity when exposed to e-cigs containing nicotine increasing the risk of infection and inflammation in the lungs (**Fig. 3**).[46]

Alterations in epithelial and sputum proteomes, airway gene expression, and mucous composition have been found with both combustibles and e-cigs. Changes in the aldehyde-detoxification and oxidative stress, immune suppression of host-defense genes; and elevation of MUC5AC, neutrophil elastase (NE), and matrix metalloproteinases (MMP)-2 and 9 have been found in allergic mouse airway samples (nasal scrape biopsies, nasal lavage, bronchoalveolar lavage [BAL], and induced sputum).[47]

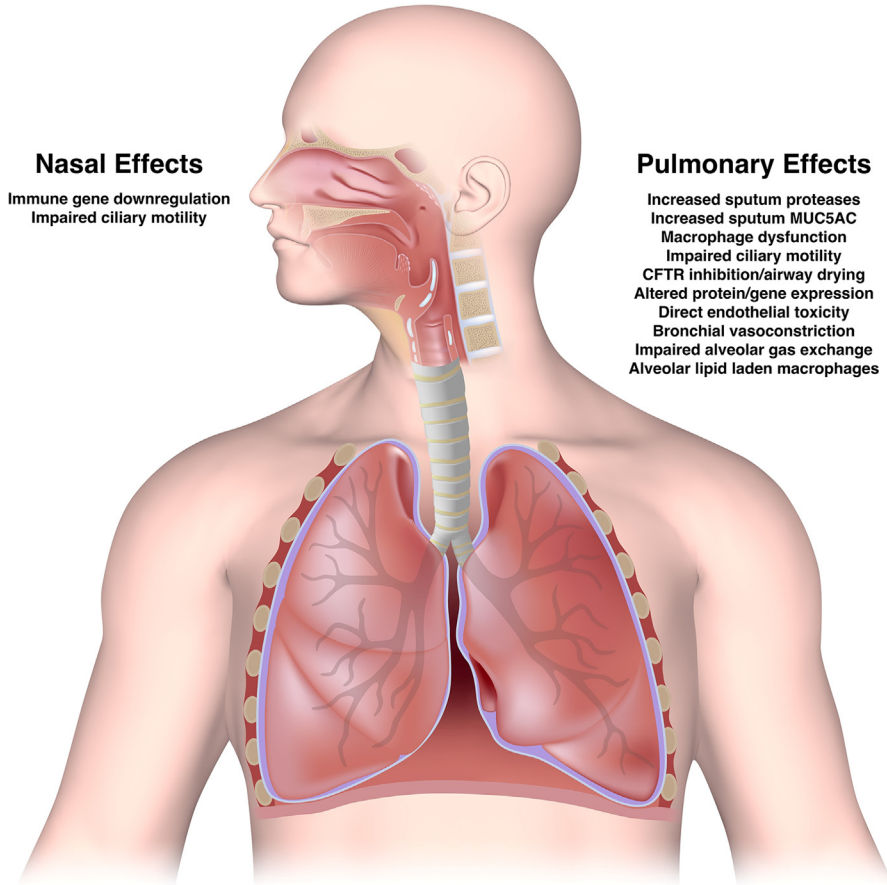

Fig. 3. Respiratory effects of e-cigarettes.

MUC5AC elevation is implicated in increased airway obstruction and nonspecific airway hyperreactivity in asthma and COPD, while NE and MMP's have been implicated in tissue damage and remodeling. Additional mucus trafficking impairment with alteration in 113 proteins of epithelial cells causes concern for mucoobstructive disease.[43,48,49]

Riedel and colleagues also showed e-cigs alter the innate immune response leading to increased neutrophilic activation with elevated neutrophil-related myeloperoxidase and neutrophil extracellular trap (NET)-related proteins. These antimicrobial innate defense markers are associated with airway inflammation and damage, suggesting that e-cigs are not a healthier alternative for cigarette users. Additionally, their study showed that peripheral blood neutrophils isolated from e-cig users were more susceptible to NET formation compared with cigarette smokers and nonsmokers, which suggests the potential risk for harmful systemic disease.[49]

Immune gene suppression occurs in e-cig users versus nonsmokers, six times more than in cigarette smokers versus nonsmokers, concerning for increased risk of infection.[47]

Gross inspection on bronchoscopy of e-cig users reveals more friable and erythematous damage when compared with smokers and nonsmokers.[48]

Spirometry has been performed immediately after vaping with mixed results. There was no significant effect on lung function when comparing active e-cig smoking or having 1 hour of passive e-cig smoking.[50] A small study compared lung function in 10 healthy adult smokers and 10 nonsmokers after using a specific nicotine-free e-cig and showed only a small reduction in FEV1 and FEF25 in smokers.[51] Another study compared lung function in 20 healthy volunteers and 10 asthmatics after a one-hour vaping session and did not show any significant change in lung function using either spirometry or forced oscillation technique.[52]

ASTHMA

Although comprehensive and longitudinal studies regarding vaping are needed, asthmatics may be an at-risk population based on early data. Many e-cig aerosol chemicals are known respiratory sensitizers and irritants. Symptoms may include wheezing, which is commonly found in adolescents and adult e-cig users.[53,54] Asthmatics were found to have significantly increased airway irritation when compared with nonasthmatic smokers and recovery took twice as long after a single session of vaping using standardized settings but FeNo was decreased after a single session of vaping.[55] Among EVALI cases, common underlying comorbidity has not been clearly identified though 22% of the EVALI cases also reported a history of asthma.[56] There have been 2 case reports of life-threatening status asthmaticus requiring extracorporeal membrane oxygenation in teenage asthmatics.[56] Additionally, 1/3 of asthmatic teenagers were at increased risk of an asthma attack due to secondhand e-cig aerosol exposure.[57] Smokers with asthma were also more likely to have alterations in respiratory resistance following the single use of e-cigs as compared with healthy controls.[58]

There is a distinct emerging association between asthma symptoms as well as an asthma diagnosis in never smokers who use e-cigs.[59,60] E-cig use was independently associated with increased school absences due to asthma in South Korea.[61] In addition, e-cig use has been independently associated with asthma in US high schoolers (adjusted odds ratio = 1.48 [1.26–1.74]).[54]

E-CIGARETTE OR VAPING PRODUCT USE-ASSOCIATED LUNG INJURY

E-cigarette or vaping product use-associated lung injury (EVALI) is an acute or subacute respiratory illness that is potentially severe and life threatening. Imaging may be variable as are pathologic features. Though not the only cause, tetrahydrocannabinol products contaminated with vitamin E acetate were strongly linked to an EVALI outbreak in 2019 and vitamin E acetate was found in most of the bronchoalveolar lavage samples of patients with EVALI.[62] Vitamin E acetate, also known as tocopheryl acetate is a commonly used thickening agent for e-liquid containing THC. As of February 2020, there were roughly 2800 hospitalized EVALI cases or deaths reported to the CDC; however, cases have subsequently declined in the past 2 years.[63] Increased public health awareness, law enforcement, and removal of vitamin E acetate from products are thought to contribute to the decline. Proposed criteria for a confirmed case of EVALI include (1) use of an ENDS product in the previous 90 days, (2) lung opacities on chest radiograph or computed tomography, (3) exclusion of lung infection including viral infections such as influenza and SARS-CoV-2 and (4) absence of a likely alternative diagnosis such as cardiac, neoplastic, or rheumatologic processes. The optimal treatment of EVALI is not known but often includes antimicrobials until infection has been excluded as well as empirical use of corticosteroids.

CONTROVERSY: RECOMMENDATIONS ON UTILIZATION

Smoking remains a clear health threat to the US as the CDC identifies nearly 500,000 deaths in the US are due to cigarette smoking annually. Additionally, they estimate that 16 million Americans suffer from combustible cigarette smoking-related disease.[64] Initially promoted as a smoking cessation tool, studies lack comparisons to other smoking cessation therapeutics including varenicline or bupropion. Compared with nonusers, daily e-cig use has been shown to increase the likelihood of sustained smoking cessation or reduced use.[65] E-cigs improved long-term smoking cessation over placebo but were less effective when compared with nicotine replacement therapy (NRT) in a Cochrane review (low-quality evidence due to significant limitations in studies).[66] Sustained smoking cessation was found in a study of adults (n = 800) in the group randomized to smoking cessation using e-cigs versus NRTs with behavioral therapy (18% vs 9.9%, adjusted relative risk: 1.75 [1.24–2.46]).[67] Although few in number in both groups, biochemical-proven reduction of 50% or more in combustible cigarette consumption was noted in more e-cig users who did not completely stop utilization compared with the NRT group (12.8% vs 7.4%, relative risk: 1.72 [1.11–2.69]). However, of the subjects from both treatment groups (e-cigs and NRT) who had sustained smoking tobacco cessation efforts for 1 year, 80% were still using e-cigs as compared with 9% using NRT. This transition from one nicotine source to another without reduction or cessation of nicotine use is disturbing as nicotine has considerable addictive and health disadvantages.

It has been anticipated that the conversion from combustible cigarettes to e-cigs will reduce the incidence of health effects such as lung cancer and chronic obstructive pulmonary disease (COPD). However, it is widely recognized that ENDS may be too novel to elucidate the long-term health and respiratory-related effects. Confounding factors in assessing health benefits may be influenced by the patient's perception of e-cigs as a healthier alternative to combustible cigarettes. Asthmatics who smoke may be encouraged to find safer alternatives to combustible cigarettes including the use of e-cigs by their health care providers.[42,68–70]

Current reported health benefits among combustible cigarette smokers who use e-cigs from surveys and small retrospective studies to include improvement in reduction in combustible cigarette use, improvement in current chronic pulmonary disease,[71] and exertional tolerance.[69] In asthmatic former cigarette smokers, e-cig utilization improves airway function, hyperreactivity, and asthma control questionnaires.[57] Unfortunately, as more time passes, details are beginning to arise as to the potential unfavorable effects of e-cigs while we await much needed large prospective studies.

SUMMARY

While there may be benefits to the utilization of ENDS in certain populations, the harms may outweigh the risks among other populations, particularly youth, never smokers, and asthmatics. According to the Centers for Disease Control and Prevention (CDC), e-cigs are not safe for youth, young adults, pregnant women, or adults who do not currently use tobacco products.[1] The balance is intricately dependent on further understanding of the long-term health effects, many of which remain elusive until further time passes, and ongoing and future studies can be completed particularly for potentially high-risk populations such as asthmatics.

CONFLICT OF INTEREST

Neither author has any conflict of interest.

FUNDING SOURCE

Neither author has any funding source.

CLINICS CARE POINTS

- Electronic nicotine delivery systems (ENDS) have been deemed a "major public health concern" by the US Surgeon General and screening for their use is imperative to ensure the delivery of appropriate patient counseling.
- Because asthmatics have airway alterations at baseline, despite potentially being a safer alternative to combustible cigarettes, vaping may place patients with asthma at higher risk of complications from use.
- Providers must have a high index of suspicion for e-cig or vaping product use-associated lung injury (EVALI), a potential life-threatening complication from vaping, in patients presenting with acute pulmonary decline.

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