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Electronic Cigarettes and Their Impact on Allergic Respiratory Diseases: A Work Group Report of the AAAAI Environmental Exposures and Respiratory Health Committee

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The explosive rise in popularity of electronic cigarette (e-cig) devices over the past decade has led to controversies over the role of these devices in smoking cessation and harm reduction from combustible cigarette smoking. Increased recognition of potential direct harms of e-cigs, including life-threatening and fatal cases of e-cig and vaping product use–associated lung injury, has emphasized the need to curb use until safety can be established. Of particular concern is the steep rise in e-cig use among teenagers and young adults who have never smoked and among individuals with underlying lung disease, such as asthma. In this report, we describe the different types of e-cig devices available, summarize the available data on the potential health benefits and detriments of e-cig use, and highlight the findings of studies examining e-cigs as smoking cessation tools. Because e-cigs have only gained popularity in the last few years, very few studies have been able to demonstrate an impact of e-cig use on harm reduction related to combustible cigarettes. Moreover, the health effects of e-cigs at a population level must be balanced against the harms of e-cig use, which include nicotine dependence and promoting initiation of cigarette use amongst "never smokers." With respect to smoking cessation, e-cigs appear to serve as switching products that may help individuals reduce or quit cigarette use, but do not address nicotine addiction. Finally, we discuss our recommendations for ways that health care providers can screen and counsel patients on e-cig use. The goal of this report is to provide health care providers with the most recent information on this topic so that they can educate patients on the potential pros and cons of e-cig use. **(J Allergy Clin Immunol Pract 2021;9:1142-51)**

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Since their introduction to the European and US markets in 2006, electronic cigarettes (e-cigs) are being used at increasing rates worldwide.[1] There is a general notion that e-cigs are less harmful than combustible cigarettes and can serve as a bridge to support smoking cessation efforts.[2,3] E-cigs are used by chronic smokers trying to quit, smokers who are looking for a nicotine fix when traditional smoking is not possible, and smokers and nonsmokers attracted by effective advertising. There has been a

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Abbreviations used
BAL- Bronchoalveolar lavage
BHO- Butane hash oil
CBD- Cannabidiol
CDC- Centers for Disease Control
COPD- Chronic obstructive pulmonary disease
E-cig- Electronic cigarette
EVALI- E-cig and vaping product use–associated lung injury
FDA- Food and Drug Administration
MCC- Mucociliary clearance
MMP- Matrix metalloproteinases
N-O-T- Not On Tobacco
NE- Neutrophil elastase
NET- Neutrophil extracellular trap
NRT- Nicotine replacement therapy
PG- Propylene glycol
SBIRT- Screening, Brief Intervention, and Referral to Treatment
THC- Tetrahydrocannabinol
VG- Vegetable glycerin

dramatic increase in e-cig use among youth over the past several years, especially in the United States; the National Youth Tobacco Survey noted that more than 5 million youth have used e-cigs.[4,5] In 2016, the US Surgeon General declared that the use of e-cigs, particularly among adolescents and young adults, represents an emerging public health concern.[6]

E-cig advocates historically cite a lack of evidence proving harm from exposure to e-cig aerosols and argue that these devices are safer alternatives to combustible cigarettes, appealing to the theory of "harm reduction."[7] Health care providers are also divided in their recommendations to patients regarding the safety of e-cig use.[8,9] However, the recent outbreak of e-cig, or vaping, product use–associated lung injury (EVALI) has highlighted the potential dangers associated with the use of these products, specifically related to the ability to customize e-cigs with additives that have not been tested for inhalational safety. E-cig use has also been associated with altered function of the respiratory and immune systems.[10-14]

Controversy still abounds among the public regarding the safety of e-cig use and the specific circumstances underlying the development of EVALI. The Environmental Exposures and Respiratory Health committee of the American Academy of Allergy, Asthma, and Immunology developed a work group report targeted to health care providers to address and clarify specific topics related to e-cig use. The intent of this work group report is to aid clinicians in the proper counseling regarding the potential benefits and known risks of e-cig use among their patients and to provide easily accessible patient education materials for use in clinical practice.

EPIDEMIOLOGY OF E-CIG USE

E-cigs were introduced in the United States in 2006 and were first touted as a tool to help smokers quit cigarettes. The evolution of e-cigs rapidly progressed from the originally introduced models of cig-a-likes (eg, e-cigs that looked like conventional cigarettes) to vape pens, box mods, and ultimately pod-based systems. Toward the end of 2015, the e-cig manufacturer JUUL introduced the first pod-based device in the United States. The sleek design of pod-based systems such as JUUL rapidly increased the use of e-cigs in teenagers and young adults.

In 2016, survey of more than 450,000 people found that 4.5% of US adults were current e-cig users.[15] Almost 2 million adults were sole e-cig users; among current users, nearly half were also current cigarette smokers (ie, dual users). In 2019, an estimated 5 million, or 27.8% of high schoolers, reported the use of e-cigs in the prior 30 days.[4] Data from the National Youth Tobacco survey showed that the most commonly selected reasons for e-cig use were use by a "friend or family member" (39.0%); availability of flavors such as mint, candy, fruit, or chocolate (31.0%); and the belief that "they are less harmful than other forms of tobacco such as cigarettes" (17.1%).[16] There is also strong evidence that teens are now more likely to transition from using e-cigs to becoming dual users of both e-cigs and combustible cigarettes.[17] Among asthmatics, there also appears to be an overall increase in e-cig use. A large survey found that from 2014 to 2017, e-cig use among asthmatics increased overall, with the largest increase (20.3%-29.1%) seen among 18- to 24-year-olds.[18] Current smokers were more likely to have tried e-cigs than former/never smokers (18-24 years, odds ratio [OR]: 11.5). Several surveys indicated that e-cig use is as prevalent or even more popular among asthmatic teenagers as compared with their nonasthmatic peers.[19-24] Middle- and high-school students with asthma who used e-cigs reported feeling that they were less likely to become addicted to e-cigs and that e-cigs were less harmful than cigarettes to both themselves and to those around them.[24] Overall, these statistics indicate that decades of public health efforts to reduce nicotine addiction among youth have been eroded with the increased use of e-cig devices.

OVERVIEW OF PRODUCTS

What is an e-cigarette?

E-cigs are devices that aerosolize a liquid solution for inhalation, most frequently containing nicotine. The process of aerosolizing an e-liquid was initially suggested to only produce water vapor, which is where the term "vaping" originated. "Vaping" is thus a misnomer as the aerosol generation process produces a complex mixture of chemicals, rather than just water vapor. Typically, an e-cig is composed of a mouthpiece, atomizer (a device which produces an aerosol from a liquid), battery, sensor, and refillable or replaceable liquid reservoir. The e-cig is typically activated by inhaling on the mouthpiece. The sensor in the e-cig then detects a change in air flow, which causes the battery-operated atomizer to aerosolize the liquid.

There are many other terms for e-cig devices that have been used or are currently being used including e-cigs, mods, vapes, tank systems, pod mods, and JUUL. JUUL products have become extremely popular with youth and young adults[25] and now dominate the US market, accounting for approximately 75% of US sales. Some of these products have become so embedded in popular culture that terms for their use have become verbs (ie, "JUULing"). These devices are streamlined and discreet in appearance; they can easily be hidden and do not produce a large vapor cloud. Contributing to the perception of reduced harm is a lack of education about the nicotine content within pod-based systems such as JUUL. In a report from *Tobacco Control*, 63% of JUUL users did not know that JUUL products always contain nicotine.[26]

What kinds of e-cigs are available?

There are many different types of e-cigs available today: (1) closed versus open systems; (2) tank mods versus pod mods.

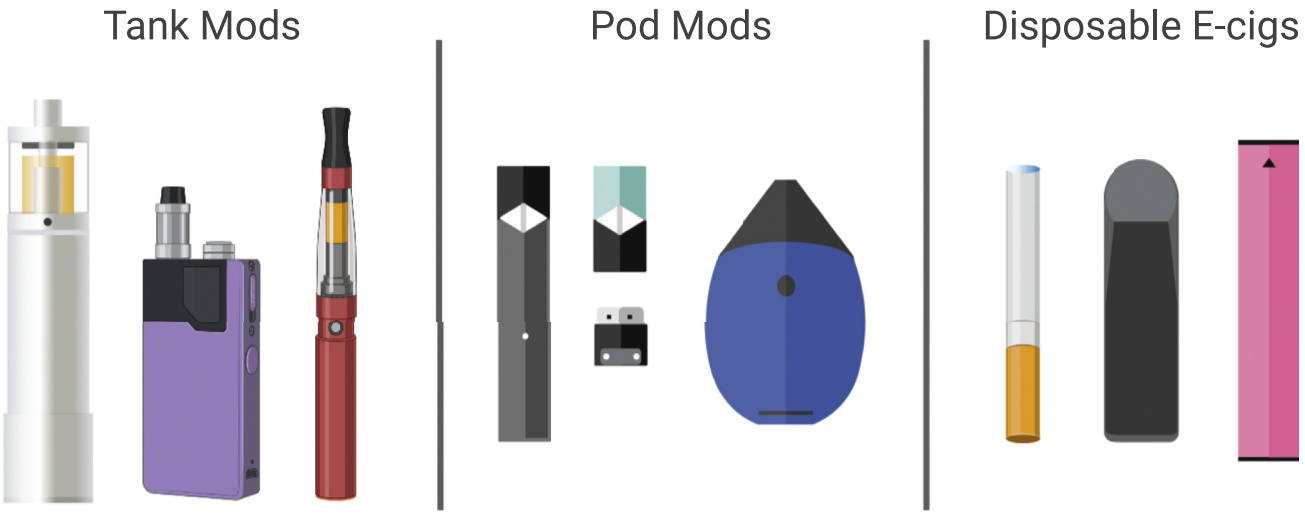

FIGURE 1. Types of e-cigarettes currently on the market (Source: CDC). Created in Biorender.com.

Closed versus open systems. Generally, open e-cig systems have refillable reservoirs for e-liquids and can be "opened" for customization, whereas closed e-cig systems use prefilled disposable e-liquid cartridges. Today, closed systems are preferred by adolescents and young adults as they are very discrete, easily concealed, and are formulated to not produce large, noticeable vapor clouds. JUUL is a current example of a closed system that is commonly used and shaped to resemble a USB drive.

Tank mods versus pod mods. Tank mods came into use in the early 2010s (Figure 1). These devices typically have a larger electronic control box (tank) that allows management of settings, such as temperature or wattage, and a reservoir that can be filled with a variety of e-liquids, which is connected to a mouthpiece. Use of tank mods is also often preferred among those trying to quit smoking or reduce nicotine exposure, as the nicotine content in e-liquids can be readily customized and are available with a range of nicotine contents (0-36 mg of nicotine).

Pod mods are newer on the market (Figure 2), but have rapidly become very popular, especially with youth and young adults. Pod mods are simple, discrete, and less expensive (shown in the Rechargeable e-cigarette section of Figure 1). JUUL is a common example of these types of devices. These devices appeal to individuals who want to hide their use in plain sight as they do not produce a large vapor cloud while still delivering high quantities of nicotine. The nicotine content can vary by type and brand. For example, JUUL is marketed most frequently with 5% nicotine, or the equivalent of 20 cigarettes worth of nicotine. Sweet and fruity flavors are often added and have been shown to play a role in youth experimentation with e-cigs.[27,28] Flavorings contained in e-cigs are currently not regulated by the Food and Drug Administration (FDA), and there have been instances where unexpected compounds have been found in e-liquids, such as nicotine present in "nicotine free" e-liquids.

POTENTIAL HEALTH BENEFITS OF E-CIG USE

Nearly half a million deaths in the United States are attributed to cigarette smoking each year, and more than 16 million Americans live with diseases caused by smoking.[29] Since their introduction, e-cigs have been marketed as reduced-harm products when compared with combustible cigarettes, which contain tar among many other chemicals. Many have argued that by reducing the number of combustible cigarettes smoked, e-cig use should result in a decline in adverse health effects, including chronic obstructive pulmonary disease (COPD) and lung cancer. Because e-cigs are relatively new products, there has been insufficient time to study whether or not introduction of e-cigs has significantly affected smoking-related health outcomes. Most of the available data on health effects are derived from surveys and small retrospective studies.

E-cig initiation among cigarette smokers has been associated with user-perceived improvement in physical endurance and pre-existing respiratory conditions[2] and reduced use of cigarettes.[30] Others have shown improvements in spirometry, airway hyperreactivity, and asthma control questionnaires scores amongst former cigarette smokers with asthma who began using e-cigs.[31] It is unclear how much influence the perception of reduced harm with e-cigs has on self-reported improvement in symptoms. Because the rise in popularity of e-cigs is relatively recent, it is unknown whether chronic use of e-cigs leads to long-term adverse health effects; however, data are now emerging on harmful effects after acute use, a topic that will be explored in detail later in this report. Large prospective studies are needed to understand the long-term health effects of e-cig use.

Transitioning from cigarettes to e-cigs does not address the problem of nicotine addiction. Nicotine itself has negative health effects that cannot be overlooked. Nicotine use has been associated with cardiovascular disease,[32] gastrointestinal disorders,[33] and serious effects to the fetus with *in utero* exposure.[34] In addition, pervasive use of e-cigs may promote nicotine use amongst "never smokers." A systematic review and meta-analysis showed strong evidence of an association between never-smoker youth initiating e-cig use and subsequent use of combustible cigarettes.[35]

The health effects at a population level are dependent on the balance between benefits (to established and former cigarette smokers) and harms of e-cig use (increase in nicotine dependence and use of tobacco products amongst "never smokers").

FIGURE 2. Popular pod mod devices currently on the market (Source: CDC). Created in Biorender.com.

Simulation modeling used to estimate the population-level benefits and harms of e-cig use in the United States[36] noted that although e-cig use would lead to smoking cessation in a proportion of current cigarette smoking adults, the number of adolescents and young adults expected to begin using combustible cigarettes through the use of e-cigs led to more harm than benefit to the population as a whole.

Use of e-cigs as smoking cessation tools

E-cig devices have also been promoted as tools to assist with smoking cessation but are not currently approved as a cessation device by the US FDA. To investigate their potential and to provide regulatory information to the FDA, studies have examined e-cigs for their potential as cessation tools. Because of variability in study design, the results of these studies have been contradictory at times. Many have failed to address the efficacy of e-cigs versus approved medical therapies such as varenicline (Chantix) or bupropion (Wellbutrin) for smoking cessation, making assessment of safety and effectiveness difficult.

The Population Assessment of Tobacco and Health data set noted that those who used e-cigs to quit smoking had an increased probability of sustained abstinence from combustible cigarettes and that daily e-cig users were more likely to quit smoking or reduce their use of combustible cigarettes compared with nonusers.[37] Many former smokers (7.6%) who had quit tobacco reported using e-cigs, and the prevalence of daily e-cig use was highest among former cigarette smokers. A Cochrane review of e-cigs and smoking cessation concluded that there was evidence that e-cigs improved smoking cessation long-term compared with placebo, with less of an effect compared with nicotine replacement therapy (NRT), though the quality of evidence was deemed low.[38] E-cigs helped smokers cut back on cigarette use to a greater degree than placebo or NRT, but the authors' enthusiasm was diminished by significant limitations of the studies reviewed.

A smoking cessation study of 800 adults randomized to e-cigs versus NRTs with behavioral support reported higher rates of sustained abstinence from combustible cigarettes in the group assigned to e-cigs compared with NRT (18% vs 9.9%, adjusted relative risk: 1.75 [1.24-2.46]).[39] In those who did not achieve full abstinence, more participants in the e-cig group showed a biochemically confirmed 50% or greater reduction in cigarette consumption compared with NRT (12.8% vs 7.4%, relative risk: 1.73 [1.11-2.69]), though few participants in either group achieved this goal. Among those with 1-year abstinence from combustible cigarettes, 80% were still using e-cigs at 52 weeks compared with 9% who were still using NRT.

The data suggest that e-cig use primarily promotes switching from one form of nicotine delivery to another, but does not assist users in overcoming nicotine addiction and continues to expose users to the known harmful effects of nicotine. In fact, manufacturers of e-cig devices note that their products are intended for use as switching products, not as cessation products for nicotine addiction.

DETRIMENTAL HEALTH EFFECTS OF E-CIGS

E-cig use has been associated with similar adverse health effects as traditional cigarettes, as well as some features that appear unique to e-cigs. Whether these detrimental effects are mediated by vehicle control compounds of e-cig liquid, such as propylene glycol (PG) and vegetable glycerin (VG), flavoring additives, or nicotine remain to be seen.

To date, only a small handful of studies have examined *in vivo* derived lung samples from e-cig users as compared with traditional tobacco smokers and healthy nonsmokers, with the objective of assessing biomarkers of harm. Several studies that have used this approach have reported a number of adverse changes in the airway, some of which were similar to those seen in smokers, whereas others were unique to e-cig users. These adverse changes include altered epithelial cell and sputum proteomes, airway gene expression, and mucus composition. Specifically, e-cig use alters the profile of innate defense genes, proteins, and proteases in airway samples (nasal scrape biopsies,

nasal lavage, bronchoalveolar lavage [BAL], and induced sputum). Among the changes seen are upregulated mechanisms such as aldehyde-detoxification and oxidative stress, suppressed host-defense genes, and elevated concentrations of pathologic mucins such as MUC5AC and elastases such as neutrophil elastase (NE) and matrix metalloproteinases (MMP)-2 and 9. Increased MUC5AC levels have important implications in the pathophysiology of asthma and COPD,[10] contributing to increased airway obstruction and nonspecific airway hyperreactivity.[40] NE and MMPs lead to increased tissue damage and remodeling.

In terms of unique effects not seen in smokers, e-cig users showed elevated neutrophil-related myeloperoxidase and neutrophil extracellular trap (NET)-related proteins, all markers of antimicrobial innate defense function that are also associated with inflammation and structural damage in chronic airway diseases such as cystic fibrosis and COPD. Six times more immune genes were suppressed in the airway of e-cig users compared with nonsmokers than in cigarette smokers compared with nonsmokers, suggesting impaired host-defense and increased risk of infection.[11] Likewise, e-cig users' peripheral blood neutrophils were more susceptible than smokers' neutrophils to NET formation, suggesting systemic effects beyond the lung in e-cig users.[12] Indeed, e-cig users have further shown altered expression of 113 epithelial cell proteins including mucins MUC5AC and MUC4, suggesting the potential for damaged mucus transport, a hallmark of muco-obstructive disease.[12-14] Visual inspection of the airway during bronchoscopy reported the presence of gross physical damage to the airways themselves in e-cig users versus smokers and nonsmokers. In addition, e-cig users' airways were visibly friable and erythematous in comparison with smokers and nonsmokers.[13]

Effects of the vehicle compounds propylene glycol and vegetable glycerin

The vehicle compounds in nicotine-containing e-liquids are PG and VG. Although advertised to have inert biological effects, they in fact have been shown to induce a number of adverse changes in *in vitro* and *in vivo* model systems. These changes include airway remodeling, significant increases in MUC5AC in epithelial cell cultures, reduced membrane fluidity, and impaired protein diffusion.[13] A pilot study of serial bronchoscopies among never smokers assessed the effect of the PG and VG components of e-cigs in the absence of nicotine or flavoring compounds.[41] Changes in urinary PG were significantly correlated with modest changes in BAL inflammatory cell counts and proinflammatory cytokines. PG/VG alone adversely affected cell viability in airway epithelial cells. It is therefore unlikely that the PG/VG vehicle is inert in terms of exerting altered responses in the airways.[42]

Effects of nicotine

The nicotine content of e-cigs typically varies between 3 and 36 mg/mL. More recent generations of e-cigs contain much more nicotine (up to 80 mg/mL), typically in a salt form to lower the pH, improving nicotine absorption and making inhalation of the product less irritating.[43,44] Nicotine has been shown to induce a number of physiological effects in *in vitro* model systems, including models of the airway. These include macrophage activation,[45] disrupted airway mucociliary clearance (MCC),[46] and altered mucus properties in primary airway epithelial cells and cell lines. Specifically, e-cigs containing nicotine adversely affected airway surface liquid, mucus concentration, and mucus viscosity, effects not seen when nicotine was absent from the e-cig exposure system.[47] These disrupted mucus properties act to reduce MCC, increasing the likelihood of persistent infection and inflammation in the lungs.

Effects of flavoring additives

Although many flavoring additives in e-cig liquids have undergone toxicity testing, including the well-known respiratory toxin diacetyl,[48] very few have been tested in inhalation models. *In vitro* exposure to commonly used e-cig flavoring chemicals and flavored e-liquids without nicotine can trigger an inflammatory and oxidative stress response and can be cytotoxic to human monocytes.[49] The flavoring agent cinnamaldehyde impaired mitochondrial respiration and glycolysis in a dose-dependent manner, temporarily reduced intracellular adenosine triphosphate levels in human bronchial epithelial cells, and rapidly yet transiently suppressed ciliary beat frequency.[50] Cinnamaldehyde and other aromatic aldehydes such as benzaldehyde and vanillin impair neutrophil function.[51]

HEALTH EFFECTS OF E-CIG USE AND SECONDHAND EXPOSURE IN ASTHMA

Although there is an ongoing debate over whether e-cigs are an effective cessation tool,[39,52] asthmatics who currently smoke combustible cigarettes are often advised by their health care providers to switch to e-cigs as a safer alternative.[30,31,53] However, several reports now demonstrate potential adverse health effects associated with concurrent e-cig use in smokers, with one study showing that dual users are more likely to report a diagnosis of asthma or COPD and are at greater risk of experiencing breathing difficulty compared with cigarette-only users.[54] In the same study, e-cig use compared with no product use was associated with greater risk of experiencing chest pain, palpitations, coronary heart disease, and arrhythmia. Asthmatic e-cig users experienced significantly increased airway irritation compared with nonasthmatic vapers, and took twice as long to recover.[55]

Asthmatics may be particularly susceptible to e-cig emissions as these aerosols contain reactive chemicals that are known sensitizers and respiratory irritants. Emerging data from the epidemiology associated with the EVALI outbreak indicate a higher-than-expected occurrence in asthmatics.[56] Moreover, we have recently described 2 case reports of adolescent asthmatic e-cig users who presented with life-threatening status asthmaticus necessitating extracorporeal membrane oxygenation.[57] Hence, the available data show that asthmatics may present a uniquely susceptible population for adverse effects of e-cig use.

Among never smokers, there appears to be a clear and reproducible association between e-cig use and asthma symptoms or an asthma diagnosis.[58] Wheezing is common among e-cig users compared with nonusers in both adolescents and adults.[59,60] E-cig use was independently associated with asthma among US high schoolers[61] and in a South Korean cohort, where e-cig use among asthmatic high-school students was associated with increased days absent from school due to asthma symptoms.[62] Recent studies have also reported increased risk of chronic respiratory symptoms among youth who use e-cigs. High-school juniors and seniors from Southern California who use e-cigs had twice the risk of reporting respiratory symptoms (chronic cough, phlegm, and/or bronchitis) compared with their

peers who do not use e-cigs, even after adjusting for dual use with combustible cigarettes or exposure to secondhand tobacco smoke. Risk of chronic bronchitis symptoms increased with frequency of e-cig use.[60]

The link between secondhand exposure to e-cig emissions and asthma has not been widely examined. Data from the National Youth Tobacco survey revealed that approximately one-third of middle- and high-school students report being exposed to e-cig aerosols in 2018, which was an increase of approximately 30% compared with the previous 3 years.[63] Data from the Florida Youth Tobacco Survey (n = 11,830) showed that 33% of 11- to 17-year-olds with a diagnosis of asthma had secondhand e-cig aerosol exposure, which was associated with an increased risk for having an asthma attack in the past 12 months.[64] Whether secondhand e-cig aerosol exposure increases the risk of developing asthma and other atopic disease remains unknown, but may be similar to what has been previously demonstrated for secondhand combustible tobacco smoke exposure (reviewed by Burbank et al[65]). In an editorial, Bousquet et al[66] postulate that there is sufficient background to support that e-cig use may boost the epidemic of atopic diseases and that this hypothesis should be tested in appropriate cross-sectional and longitudinal epidemiologic studies. A study is currently underway to investigate how secondhand e-cig exposure impacts heart and lung health in adults and children who are nonusers.[67]

HEALTH EFFECTS OF VAPING TETRAHYDROCANNABINOL (THC) PRODUCTS

The increased use of both medical marijuana (legal in 33 states) and recreational marijuana (legal in 11 states and the District of Columbia as of December 2019) has presented new opportunities for the vaporization of THC-containing products. The use of marijuana vaporizers and their main compounds including THC, cannabidiol (CBD), and butane hash oils (BHO) dates back to the 1980s. However, their use has become increasingly popular since 2014, especially in teens and young adults, due to the ability to include marijuana products in e-cigs. Prefilled cartridges of cannabinoid concentrate can be loaded into e-cig devices.[68,69] In addition, many cannabinoid-containing cartridges can be combined with artificial flavors and scents, including vanilla, apple, chocolate, cherry, and many others.[69] Recent reports show that 30% to 77% of vapers use THC cartridges in the United States,[70] likely owing to ease of accessibility and lack of federal and local regulations, benefiting both the legal and illegal markets for these cartridges.[70,71] Marijuana and THC-containing vaporizers produce their psychoactive effects within a few minutes.[72]

Inhalation of THC and BHO has been associated with organizing pneumonia and pneumonitis, respectively.[73] Chemical products added to modify the taste and smell of products containing THC, CBD, and BHO such as diacetyl, 2,3-pentanediol, and acetoin have been associated with bronchiolitis obliterans. The short- and long-term health effects of inhaling these chemical products are currently incompletely understood.[74,75] Some cannabinoid-containing products also include pesticides, which are likely used in the illegal production of marijuana.[76] Many of the pesticides found in cannabinoid-containing products are classified as carcinogenic substances.[77]

TABLE I. US CDC and FDA recommendations: e-cigarette or vaping products

Populations that should not use e-cig or vaping products
Youth and young adults
Women who are pregnant
Adults who do not currently use tobacco products
Populations that already use e-cig or vaping products
Do not buy these products off the street (eg, e-cig products with THC or other cannabinoids)
Do not modify e-cig products or add any substances to these products that are not intended by the manufacturer
Do not add vitamin E acetate to e-cig or vaping products
Adult smokers who are attempting to quit should use evidence-based treatments, including counseling and FDA-approved medications. If you need help quitting tobacco products, including e-cigs, contact your doctor or other medical provider

CDC, Centers for Disease Control; *FDA*, Food and Drug Administration; *THC*, tetrahydrocannabinol.

E-cig and vaping product use–associated lung injury (EVALI)

As of February 2020, more than 2800 cases of EVALI have been reported to the Centers for Disease Control (CDC) from 50 states, the District of Columbia, Puerto Rico, and the US Virgin Islands, resulting in 68 deaths. Seventy-seven percent of those diagnosed with EVALI are under 35 years of age (median age, 24 years) and 68% are male.[78] The typical clinical presentation of EVALI includes respiratory and gastrointestinal complaints; presence of systemic inflammation, particularly marked leukocytosis; and chest imaging showing bilateral, multifocal ground-glass opacifications. Lipoid pneumonia had been suggested as the responsible pathophysiology based on several cases where BAL fluid from admitted patients revealed the presence of lipid laden macrophages.[56,79-81] However, a recent study described the pathologic examination of lung biopsies from patients with EVALI where the findings were more consistent with airway-centered chemical pneumonitis rather than lipoid pneumonia.[82] In the majority of cases (more than 80%), patients vaped products containing THC, the primary psychoactive component of marijuana. EVALI has been linked to vitamin E acetate, a thickening agent found in most THC-containing e-liquids.[83] The dramatic rise in EVALI related to THC-containing vape devices has prompted the FDA to prepare upcoming regulation on the use and commercialization of vaping devices that contain substances other than nicotine. Simultaneously, several states are already working on a series of regulations to control these devices[84] as well as flavorings.

OTHER REPORTED HEALTH EFFECTS

In August 2019, the FDA announced that it had received 127 reports of seizures or other neurological symptoms possibly related to e-cigs. There are higher reports of seizures particularly among younger users.

RECOMMENDATIONS ON COUNSELING PATIENTS ON THE USE OF E-CIGS

The CDC and the FDA announced in September 2019 that e-cig and vaping product use should be avoided while they

investigate the etiology of EVALI cases. Their specific recommendations are described in Table I.

Approach to counseling

Screening, Brief Intervention, and Referral to Treatment (SBIRT) allows health care providers to systematically screen and assist people who may not seek help for a substance use problem. SBIRT is an evidence-based practice used to identify, reduce, and prevent problematic use, abuse, and dependence on a variety of substances. SBIRT is being actively tested in pediatric emergency departments to promote parental tobacco cessation.[85] This general approach may be applied to e-cig users who present to outpatient providers for routine care. In Table II, we have highlighted general suggestions regarding counseling for e-cig or vape use.

SCREENING

The initial conversation centers on asking if the patient and/or family members use e-cigs, or vapes, as part of a routine social history. Many teens and young adults do not perceive e-cigs as tobacco products, and thus the general question "do you use tobacco products?" will not capture e-cig users. In addition, many adolescents do not consider JUUL and JUUL-like products to be e-cigarettes, so more specific questions may be necessary.

If they do use e-cigs, the next query should focus on asking what kind of products and/or specific brand they use. For example, many young adults use JUUL, teens prefer the disposable Stigs, and others like to customize their e-liquids and their devices. E-liquids can be purchased online, through storefronts, and/or through informal channels and can also be mixed at home. You can ask questions about the flavors that are being used, the nicotine content, and whether or not they use CBD- or THC-containing liquids. Infographics with different e-cig devices can be posted in clinic rooms to allow for easier identification of devices, similar to asthma inhaler identification charts commonly used in clinics. We have provided an example of an infographic that can be used to assist in identifying devices: https://www.med.unc.edu/cemalb/files/2020/12/2020_12_18-HickmanMethodVapingQuizCompressed.pdf.

The next set of questions center on why the products are being used. Some adult smokers use e-cigs to transition away from combustible cigarettes. Adolescents may perceive that e-cig use allows them to bond with their peer group. The answers derived from these questions will inform the intervention/educational section.

BRIEF INTERVENTION

The intervention stage involves engaging the patient in a short conversation, providing education, feedback, motivation, and advice. The end of this conversation will include an assessment for readiness to change and enhance motivation for the change. Among patients who do not use e-cigs, we recommend a short conversation focused on health effects of e-cig use.

For e-cig users, a provider can begin the conversation with "What do you like about vaping? What don't you like?". This will move the conversation toward educating regarding pros and cons of e-cig use. Examples of pros and cons are found in Table II.

TABLE II. Screening Brief Intervention Referral to Treatment (SBIRT) counseling strategy

Screening	1. Do you vape, JUUL, or use any e-cig products? 2. Do you vape marijuana, dab, or vape hash oil? 3. What motivated you to start vaping? 4. What device or devices do you like to use? https://www.med.unc.edu/cemalb/files/2020/12/2020_12_18-HickmanMethodVapingQuizCompressed.pdf	
Brief intervention	Vaping pros: • Smells good • Perceived as harmless • People who smoke combustible cigarettes report feeling better when they switch to vaping • May be helpful for smoking cessation in some people	Vaping cons: • Lung injury and or death (EVALI cases) • Exploding lithium batteries with physical injury • Seizures in children • Newly addicted to nicotine • More likely to start smoking combustible cigarettes • Nicotine switch product, not as good for cessation
Referral to treatment	1. Smoking cessation programs 2. Nicotine replacement therapy 3. Wellbutrin and Chantix (adults only) 4. TRUTH initiative for teens https://truthinitiative.org/our-top-issues/vaping-issue Text "QUIT" to (202) 804-9884 5. N-O-T Program for teens aged 14-19 https://www.lung.org/quit-smoking/helping-teens-quit/not-on-tobacco	

EVALI, E-cig and vaping product use–associated lung injury.

REFERRAL TO TREATMENT

Among those ready for change, we recommend referral to smoking cessation programs. Several health care organizations will accept referrals for e-cig use as part of their smoking cessation programs. Nicotine addiction appears to be better addressed through FDA-approved NRT (like the patch or the gum), along with medications such as bupropion (Wellbutrin) and varenicline (Chantix). An important limitation of these therapies is that they are only FDA-approved for ages 18 and older. Bupropion and varenicline have been found to be ineffective in youth and young adults using e-cigs with nicotine and was accompanied by psychoactive effects including suicidal ideation.[86] In fact, the FDA noted in 2019 that varenicline is not recommended for youths 16 years and under as it did not significantly increase abstinence rates.[87] Regardless of the patient population, pharmacologic interventions are most effective when added to cognitive-behavioral counseling and support.

For children, treatment is limited to app- and text-based quit programs developed by the Truth Initiative and other organizations such as the American Lung Association. The Truth initiative has established resources specifically for teens. Teens who text "QUIT" to (202) 804-9884 will start receiving text messages offering assistance and guiding them to resources. In addition, the American Lung Association established a 10-week voluntary quit smoking program for teens aged 14 to 19 years called Not On Tobacco (N-O-T). The N-O-T program reports that 90% of teens who participate in the program cut back or quit tobacco altogether. A link to this program's website is provided in Table II. Patient education materials are available for distribution by the FDA's tobacco education resources and by the American Thoracic Society: https://digitalmedia.hhs.gov/tobacco/print_materials/search?tag=E-cigarettes%2Fvaping and https://www.thoracic.org/patients/patient-resources/resources/vaping-electronic-nicotine-delivery-systems.pdf.

CONCLUSIONS AND FUTURE DIRECTIONS

E-cigs have been marketed as reduced-harm products, and it has been argued that their continued availability may lessen the burden of disease and disability associated with smoking cigarettes. However, others argue that the risk of e-cig use and nicotine addiction among youth far surpasses the potential benefit of e-cigs. The long-term health effects of e-cig use and secondhand e-cig exposure are unknown.

We do know that among those who smoke cigarettes, e-cig use primarily promotes switching from one form of nicotine delivery to another, while only minimally supporting complete recovery from nicotine addiction. We also know that we need to correct the perception that e-cig use represents inhaling a harmless water vapor, especially for patients with asthma, as short-term and basic research studies have demonstrated that e-cig use can alter airway and cardiovascular physiology. Easy to understand schematics and illustrations of the e-cig devices and components of e-liquids are important for effective patient education.

In addition, we know that nicotine is highly addictive, and that the earlier in life use of nicotine products begins, the more difficult it is to quit later. Teens are now more likely to transition from using e-cigs alone to becoming dual users of e-cigs and combustible cigarettes.[17] Furthermore, some e-cigs have higher nicotine content and nicotine that tastes less harsh than smoking a regular cigarette, increasing the addictive potential. To prevent youth use, broader societal efforts are being considered, including the banning of flavored e-cig products, banning online sales of e-cigs and e-liquids, increasing the legal age of use to 21 years, and restricting use in 100% smoke-free areas such as schools.

EVALI cases have highlighted the dangers of seemingly harmless ingredients in e-liquids, such as vitamin E acetate. Moreover, manufacturing labels are not always comprehensive in regard to e-liquid and vaping product constituents.[88] The ability to customize devices and e-liquids with THC-containing products may additionally increase the risk of sometimes fatal lung disease.[89]

In conclusion, a multifaceted approach is needed to reduce e-cig use and nicotine addiction worldwide. Regulatory authorities have and will continue to experience challenges in restricting the sale of these products. Enforcement of existing laws is problematic given the availability of online vendors and informal sources. As health care providers, we can engage and educate our patients and their families regarding e-cig use during routine encounters to provide factual information regarding the perceived benefits and risks of these devices.

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