

REVIEW ARTICLE



A review of toxic effects of electronic cigarettes/vaping in adolescents and young adults

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ABSTRACT

In this review, we examine the known and suspected toxicity of electronic cigarettes (e-cigarettes) in adolescents and young adults, to improve awareness of risks and identification of complications of their use. The use of e-cigarettes, or “vaping,” is exploding among the pediatric population. E-cigarettes heat a solution containing a psychoactive compound, most commonly nicotine or tetrahydrocannabinol (THC), along with flavorings and other additives to a vapor, which users inhale. Since their introduction in the early 2000s, e-cigarette use is now prolific among youth, per the Monitoring the Future survey, with over 40% of high school seniors reporting use within the past year. Adolescents are vulnerable to the risks of e-cigarettes, as they are targeted as new consumers with advertisements and flavoring compounds, and are not utilizing them as a means to smoking cessation. The pulmonary risks of vaping are rapidly emerging, with the most immediately alarming being the condition electronic-cigarette/vaping associated lung injury (EVALI). Additionally, there have been more recent studies showing extrapulmonary effects including cardiovascular, immunologic and neuro-developmental effects. Many of these effects are likely dose-dependent. Public health efforts are urgently needed to decrease or eliminate new e-cigarette initiation, and support should be established to assist current e-cigarette users with cessation. We strongly advocate for the elimination of e-cigarette flavorings and advertising directed at adolescents, and call for physicians to be cognizant of this expanding epidemic.

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Introduction

Vaping, or the use of electronic cigarettes (e-cigarettes) which vaporize chemical substances, primarily nicotine or tetrahydrocannabinol (THC), the active component of cannabis, for inhalation has reached striking proportions among pediatric populations. The Monitoring the Future survey, sponsored by the National Institute of Health, Institute on Drug Abuse, reported in 2019 that 40.5% of 12th graders (95% CI 37.3–43.8%) reported vaping in the past year (Johnston et al. 2019; Miech et al. 2019; NIDA 2019). Pulmonary harms of vaping have more recently been described and in 2019 the outbreak of e-cigarette/vaping associated lung injury (EVALI) emerged, with the median age of 19 years in cases initially reported (Layden et al. 2020). Increased use among middle and high school students appears to be driven by advertising campaigns and by flavored products designed to attract adolescents and young adults (Dai and Hao 2016). The risks to the pediatric population are especially important as many adolescents who vape are nicotine-naïve and are not using e-cigarettes as smoking cessation devices, as they were originally marketed. The public, in general, believes that vaping carries minimal health risks (Anand et al. 2015), which has further contributed to its broad uptake, thereby reversing prior persistent decline in

nicotine use in the US, a prior public health success. We discuss the pathologic effects of vaping and the particular challenges that this preventable injury presents in adolescents and young adults.

Brief history of nicotine and tobacco

Tobacco use originated in the temperate regions of the Americas, and native populations had widespread use of tobacco, including for cultural, religious, and medical reasons. Use significantly increased through the 1800s and 1900s, until the dangers became well-known. In the mid-1900s, the causative relationship between chronic diseases including cardiovascular and lung diseases and many cancers and tobacco smoke was established (Dani and Balfour 2011). Since then, tobacco use has dropped significantly in the US, from an estimated 42% in 1965 to 19% in 2017 (Wang et al. 2019). Worldwide, tobacco use remains a significant public health concern, with an estimated 9% of deaths attributed to smoking (Dani and Balfour 2011). In the late twentieth and early twenty-first century, regulations including in the USA and other countries placed heavy restrictions on advertisements of cigarettes and tobacco products with a subsequent decline in the use of tobacco by adolescents under 18 (Braverman and Aarø 2004; Lovato et al. 2011).

In the midst of the decline in overall tobacco use, e-cigarettes arrived as a new vehicle for nicotine addiction, initially marketed for smoking cessation as a safer alternative to combustible cigarettes. E-cigarette products rapidly rose in popularity and the prevalence of use is concerning, especially among adolescents. Invented in 2003, e-cigarettes became widely available in the 2010s, and their use by adolescents has notably increased to a reported 40.5% of 12th graders in 2019 (Miech et al. 2019).

Unique challenges for adolescents

Adolescents are uniquely susceptible to vaping. Historically, adolescents were targeted with cigarette advertisement and had notably higher rates of initiation of tobacco usage. In the current decade, teen use of vaping products has skyrocketed, most recently over 40% of high school seniors reporting use within the past year (Dai and Leventhal 2019; Gentzke, Creamer, et al. 2019; Johnston et al. 2019). Over 24 million adolescents are exposed yearly to vaping advertisements (Duke et al. 2014; Mantey et al. 2016), which often feature adolescents (Duke et al. 2014), and as e-cigarette companies have spent more money on advertising, we have seen an increase in adolescent vaping (Kim et al. 2014). Although e-cigarettes were initially introduced as products used for smoking cessation, many current advertisements focus on teenagers who are not current users of nicotine products; for example, there are over 1 million posts on Instagram regarding e-cigarettes, with many ads generated by e-cigarette producers. These posts emphasize the “culture” of e-cigarette consumption and emphasize that vaping is an “adult behavior,” including one brand with the tag line “We’re all adults here. It’s time to take back your freedom”

(Duke et al. 2014). A larger number of advertisements have a significant sexual component, often posted by female models in suggestive poses or clothing (Ritter 2015). JUUL, the largest e-cigarette company, has been cited by the FDA with concerns that they have been marketing directly to children, including a report that a JUUL representative gave a lecture directly to high-school students advocating that JUUL is “totally safe” (FDA 2019). Although this marketing strategy appears to be at odds with a product intended for smoking cessation, it has been financially successful: in 2018, JUUL was partially sold to Altria (a cigarette manufacturer) with a valuation of \$38 billion dollars.

Flavor and flashy devices increase the attraction for adolescents. An expanding culture surrounding the development of new flavors and varieties has also erupted. Websites advertise many custom flavorings, including “Strawberry Vanilla Cupcake Milkshake,” “Chocolate Marshmallow,” and “Half-Baked Snickerdoodle” (MigVapor 2019). This marketing strategy mimics “flavored cigarettes” advertising campaigns that targeted adolescents (Carpenter et al. 2005). A dislike of the taste of e-cigarettes has also been linked with discontinuation of vaping in adolescents, incentivizing the development of attractive flavors to increase adolescent vaping (Kong et al. 2015). Large and flashy devices, often combined with e-liquid designed to make an opaque vapor cloud, draw attention to the users and can be used by teens looking to attract attention and perform for others. Thousands of online videos demonstrate “vaping tricks,” including forming large clouds, and shapes that are attractive to adolescent users. E-cigarette advertisements significantly increase the prevalence of e-cigarette use among adolescents (Dai and Hao 2016; Stroup and Branstetter 2018).

Components of e-cigarettes

The liquid added to e-cigarettes to be vaporized (known as the “e-liquid”), contains at least three major ingredients: psychoactive agents, solvents, and flavoring compounds, which all have potential health risks, either alone or in combination.

The most common psychoactive ingredient in e-liquids is nicotine. Nicotine is a naturally occurring alkaloid that is highly addictive and has been consumed by humans for hundreds of years. The nicotine in vaping liquid can come in one of two chemical formulations. Nicotine freebase is the unprotonated form, often called “pure nicotine,” and can be easily vaporized by heat for absorption through the lungs. However, high concentrations of nicotine freebase are unpleasant to consume, leading to the development of an alternative formulation, nicotine salt. This nicotine is in its protonated state, complexed with an acid, primarily benzoic acid. This crystal is then dissolved in the vaping fluid. This benzoic acid salt allows e-liquid formulation to contain far higher nicotine concentrations, up to 50 mg/mL, with concomitant increases in the nicotine dose received by the user resulting in increasing addictive potential (Goldenson et al. 2017). Alternatively, e-liquids can contain THC, with a wide variety of THC concentrations and formulations.

The primary ingredient of e-liquids in terms of volume is a solvent containing propylene glycol (PG) and vegetable glycerin (VG) (Varlet et al. 2015). These liquids perform the dual role of diluting the nicotine to its desired concentration and allowing a consistency which can be easily vaporized, and the ratio between them affects nicotine delivery. In addition, the proportion of PG to VG affects the “cloud formation” from exhaled vapor, where VG is primarily responsible for generating the thickness of the “cloud.” Due to its higher viscosity and density, e-cigarette users report liquid containing elevated concentrations of VG damages the e-cigarette vaporizer and diminishes the impact of added flavorings (Taylor 2017; Kosmider et al. 2018).

Over 7000 e-liquid flavoring agents are commercially available, and flavoring mixtures often comprise proprietary blends of chemicals with uncertain toxicologic profiles (Allen et al. 2016). Diacetyl (2,3-butanediol) which has been used in the food flavorings industry and in e-liquids due to its buttery flavor and favorable chemical properties has been associated with bronchiolitis obliterans in an occupational outbreak among microwave popcorn workers (Kreiss et al. 2002). Terpenes, another category of flavoring chemicals often used in e-liquid, are naturally occurring aromatic oil derivatives of isoprene (Varlet et al. 2015; Meehan-Atrash et al. 2017). The available data on the toxicity of terpenes when inhaled are minimal and generally limited to turpentine, which is a combination of different terpene components and has been associated with lung necrosis in pediatric patients (Khan et al. 2006). There is also concern regarding the production of toxic aldehydes including acrolein, formaldehyde, and acetaldehyde during the heating of the e-liquid, but the clinical importance of this is not yet known (Khlystov and Samburova 2016).

The e-liquid must have specific physiochemical properties to enable e-cigarette function. Most e-cigarettes have a tank or pod to hold the e-liquid attached to a coil which heats and vaporizes the components. Liquid that is too viscous can obstruct the heating elements or not vaporize correctly. A commonly used thickening agent for THC-containing e-liquid is vitamin E acetate (or tocopheryl acetate). The CDC has identified vitamin E acetate as “strongly linked to the EVALI outbreak” (CDC 2020). In September of 2019, New York State Department of Health reported the detection of vitamin E acetate in a number of samples of THC-containing e-liquid which had been used by individuals who later developed pulmonary symptoms (Sun 2019). Bronchoalveolar lavage (BAL) samples obtained from 51 patients showed the presence of vitamin E acetate in 48 of 51 BAL samples (Blount et al. 2020).

Finally, understanding the toxicology of e-liquids is further complicated by unregulated and homemade e-liquids. Some users view e-cigarettes as a hobby, making their own e-liquids and custom manufacturing e-cigarette machinery and selling them to members of online e-cigarette communities via Instagram or Twitter (Mackey et al. 2015). The contents of these e-liquid formulations are completely unknown and unregulated.

Pathologic effects of vaping/e-cigarette use

Although the outbreak of cases in the USA of pulmonary injury associated with e-cigarette use has accelerated toxicology studies, systematic data regarding adverse effects from vaping remain incomplete. We will report what is known, and identify areas where ongoing research continues.

E-cigarette/vaping associated lung injury

The Center for Disease Control and Prevention (CDC) has received reports of over 2800 cases of lung injury from vaping, with over 60 confirmed deaths in an outbreak that began in 2019 (CDC 2020). EVALI cases are identified based on CDC diagnostic criteria, including recent vaping, pulmonary infiltrates on chest imaging and the absence of pulmonary infectious findings, although it is certainly important to note that many patients with the diagnosis of EVALI use other inhalational substances (Siegel et al. 2019). Many questions remain regarding causes, diagnosis, and management of EVALI cases. Pathologic reports from these cases have shown a variety of findings consistent with acute toxic lung injury, including fibrinous pneumonitis, diffuse alveolar damage, or organizing pneumonia (Sommerfeld et al. 2018; Arter et al. 2019; Butt et al. 2019; Layden et al. 2020). The patterns of injury described are consistent with toxic/chemical induced lung injury. Vitamin E acetate and THC containing vaping products have been “strongly linked” to the outbreak, but 15% of patients with EVALI report using only nicotine containing products (CDC 2020). The mechanism of injury is not clearly understood.

Patients diagnosed with EVALI often have a variety of abnormalities seen on chest imaging studies, including X-ray and computerized topography (CT). The following radiographic findings have been described in the setting of EVALI including diffuse bilateral ground-glass opacities, areas of consolidation, centrilobular nodules, septal thickening, pleural effusions, crazy paving, and the atoll or reverse halo sign (Henry, Kanne, et al. 2019; Henry, Kligerman, et al. 2019; Mukhopadhyay et al. 2020). These findings are not specific to any one specific pathologic entity thus posing additional diagnostic challenges in cases of possible EVALI and thus must be interpreted in the clinical context.

A majority of EVALI patients used e-liquids containing THC or nicotine, often obtained from non-regulated sources. Many of these e-liquids have been determined to contain vitamin E acetate (Christiani 2020; Layden et al. 2020; Pray et al. 2020), typically used as a thickening agent, especially in THC-containing e-liquid obtained from unregulated sources. Some of these THC e-liquids have been branded as “Dank Vapes,” however, this branding has been copied by many other products on the black/gray markets (Grady 2019).

Currently, due to studies showing vitamin E acetate in BAL, as well as the detection of vitamin E acetate in e-liquids used by multiple outbreak clusters, it is felt by the CDC to be a primary cause of the EVALI outbreak (Blount et al. 2020; CDC 2020; Pray et al. 2020). Vitamin E acetate has been shown to disrupt phospholipid bilayers (Kamal and Raghunathan 2012), and this disruption has been

hypothesized to decrease the effectiveness of pulmonary surfactant (Blount et al. 2020).

Removing the toxic exposure is of primary concern, and cessation of vaping should be strongly emphasized to patients. Most patients show clinical improvement with cessation of vaping (Kalininskiy et al. 2019). Patients with severe pulmonary dysfunction, including hypoxia or respiratory distress, should be admitted to the hospital for further care. Corticosteroids have been described to improve symptoms. Sixty-five percent of patients in Wisconsin noted “respiratory improvement was due to the use of glucocorticoids,” but this is confounded with the concurrent cessation of vaping in many patients (Layden et al. 2020). This has led to the current recommendation from the CDC to support corticosteroid use in most patients, with consideration of possible infectious risks while alternate infectious causes are being evaluated (Siegel et al. 2019).

Ongoing follow-up for these patients after their initial diagnosis is also critical. Many patients have continued vaping after developing EVALI, and further assistance in cessation may be needed. Patients should have close follow up with either primary care physicians or pulmonary specialists.

Possible pulmonary injury from flavoring chemicals, including diacetyl

Diacetyl is an organic compound used in the food and flavoring industries for its flavor profile. Most manufacturers of e-liquid have sought to make their products uniquely marketable using proprietary blends of flavors, and diacetyl had been added to e-liquid formulations, including flavorings potentially appealing to children such as CooCoo Coconut, Tutti Frutti, and others (Allen et al. 2016).

In 2000, a possible association between bronchiolitis obliterans and occupational exposure to microwave popcorn manufacturing (“popcorn lung”) was first recognized (Kreiss et al. 2002). While the exact cause of the outbreak of bronchiolitis obliterans is unclear, epidemiological and animal studies identified diacetyl as a possible cause (Hubbs et al. 2002; Fedan et al. 2006). The National Institute of Occupational Safety and Health “determined that artificial butter flavorings added to the popcorn was responsible for causing the disease” (NIOSH 2017). The hypothesized mechanism of injury was thought to arise from Schiff base condensation of the diacetyl ketone group with amine side chain components of proteins. However, there are some concerns with this causal determination, as diacetyl has also been detected in cigarette smoke at high levels, without significant increases in reports of bronchiolitis obliterans in tobacco smoking populations (Pierce et al. 2014). Tobacco smoke also contains a large number of other chemicals which may distort the pathologic effects (Stedman 1968). Since the announcement of the concerns for diacetyl respiratory exposure, significant occupational protections have been established for workers in plants using diacetyl.

E-liquid producers have started advertising many products as “diacetyl free.” However, multiple e-liquid preparations, including some advertised as “diacetyl free,” contained

measurable amounts of diacetyl (Farsalinos et al. 2015; Allen et al. 2016; Rutledge 2018). A case of bronchiolitis obliterans organizing pneumonia in a patient using e-cigarettes has been described, but the chemical cause remains unclear (Mantilla et al. 2016).

Obstructive lung diseases, including asthma

Limited studies show that e-cigarettes may worsen obstructive lung diseases. Survey data from a population of high school students in South Korea suggested that vaping was associated with increased odds of being diagnosed with asthma and with more missed days of school secondary to asthma (Cho and Paik 2016; Kim et al. 2017). In a study of 2086 adolescents, participants who had previously vaped were twice as likely to experience symptoms of bronchitis as compared to those who had never vaped (McConnell et al. 2017). In a laboratory setting, e-cigarette use altered pulmonary function and inflammation in asthmatic patients (Kotoulas et al. 2020). Additionally, animal studies in mice demonstrated mice exposed to e-cigarette fluid had increased airway hyperactivity, mucin production, cytokine expression, protease expression, and distal airway enlargement (Garcia-Arcos et al. 2016). When these products are used for tobacco cessation, users report improvement in asthma symptoms (Solinas et al. 2020).

Passive exposure to e-cigarette emissions

Exposure to secondhand smoke from e-cigarettes has been shown to carry both pulmonary and extrapulmonary risks. Adolescents with exposure to secondhand e-cigarette smoke were found to have increased odds of self-reported asthma exacerbations (Bayly et al. 2019), and passive exposure to e-cigarette emissions induces broad changes in respiratory physiology, including pulmonary inflammation denoted as an increase in the fractional exhaled nitric oxide (Tzortzi et al. 2018). Changes in air quality measures have also been observed with vaping, with increases in particulate matter even in locations with adequate ventilation (Schober et al. 2014). The delivered nicotine dose from passive e-cigarette exposure, as measured from serum cotinine concentrations, is similar to that of conventional cigarettes (Flouris et al. 2013; Ballbè et al. 2014). Overall, these risks are similar to those caused by passive tobacco smoke exposure, and thus steps should be taken to decrease adolescent secondhand exposure risk, including limiting vaping in businesses, restaurants, and other enclosed spaces.

Cardiovascular effects

There are many significant cardiovascular dangers of traditional cigarettes, including increased risk of myocardial infarctions, chronic vascular disease and heart failure. Daily vaping is associated with increased risk of myocardial infarction, but this risk is relatively less than daily conventional cigarette use (OR 1.79 with 95% CI = 1.20, 2.66 for vaping, OR 2.72 with 95% CI = 2.29, 3.24 for conventional cigarettes)

(Alzahrani et al. 2018). The use of e-cigarettes has also been associated with increased heart rate and blood pressure (Cooke et al. 2015), signs of oxidative stress (Carnevale et al. 2016), and impaired vascular flow (Antoniewicz et al. 2019). There are also other biochemical cardiovascular effects seen from vaping. Mice exposed to nicotine-containing e-cigarettes had decreased left ventricular fractional shortening and ejection fraction, and cardiomyocytes showed structural features concerning for cardiomyopathy (Espinoza-Derout et al. 2019). Endothelial cells were exposed to a variety of e-liquids, with a variety of resulting cell damage, including lower cell viability and increased reactive oxygen species formation (Lee et al. 2019). When used for smoking cessation, vaping may decrease the cardiovascular risk for tobacco users (Glasser et al. 2017), however, in adolescent populations who are previously nicotine-naïve and not using the e-cigarettes for tobacco cessation, the risk-benefit consideration shifts significantly.

Immune system effects

In vitro studies have shown concerns regarding possible impaired antimicrobial and antiviral effects (Chen et al. 2019). Compared to non-vaping controls, adults who vaped had increased platelet-activating factor receptor. As pneumococci use this receptor to adhere to host cells, vaping may increase the risk for increased bacterial burden and pneumonia (Miyashita et al. 2018). Human tracheobronchial epithelium infected with human rhinovirus and exposed to e-cigarette vapor demonstrated increased viral load, increased inflammatory cytokines, and decreased defense molecules (Wu et al. 2014; Chen et al. 2019). These studies may be limited by the inequivalent dosing methods *in vitro* as compared to real-world use.

Genetic and developmental effects

In vitro, e-cigarette emissions have been shown to exert effects on cell genetics, growth, and development; however, interpretation of clinical implications is limited by the *in vitro* dosing rather than human use patterns. Newborn mice exposed to e-cigarette vapor had decreased weight gain as compared to controls, as well as decreased alveolar growth with observed reduction in postnatal lung growth (McGrath-Morrow et al. 2015; Chen et al. 2019). Examination of immune-related genes via nasal scraping demonstrated that e-cigarette exposure decreased expression over 300 immune-related genes (Martin et al. 2016). The clinical effects of these changes in gene regulation are unknown.

Connections to other drug use, including conventional cigarettes

Electronic cigarettes may lead to other substance use. Adolescents who used e-cigarettes have increased prevalence of future cigarette smoking (Soneji et al. 2017). The odds of initiating cigarette use is over six times greater in those who used e-cigarettes (Berry et al. 2019), and nicotine has been

associated with biochemical and functional changes linked to subsequent drug use. This includes effects on the dopaminergic mesolimbic pathway, which releases dopamine in the nucleus accumbens and facilitates reward feedback pathways, as well as the endocannabinoid and endogenous opioid systems (Ren and Lotfipour 2019). Increased exposure to e-cigarette vapor may counteract public policies to limit secondhand smoke and may reestablish smoking behaviors as commonplace and publicly accepted (Gentzke, Wang, et al. 2019). Data from 15 to 24 year old patients from the 2017 Canadian Tobacco, Alcohol and Drugs Survey demonstrated that vaping was significantly correlated with marijuana and alcohol use (Mehra et al. 2019). A systemic review and meta-analysis in 2019 showed that adolescents and young adults who reported vaping had a 3.5 times higher odds of marijuana use (Chadi et al. 2019). An analysis of the National Youth Risk Behavior Survey also found a correlation between e-cigarette use and the use of marijuana and alcohol and the misuse of prescription medications (Curran et al. 2018). Adolescents may not understand how to interpret nicotine concentration of vaping liquid, and this may lead to increasing nicotine consumption, ultimately culminating in nicotine addiction. In one study, 39% of adolescents thought that JUULs were not e-cigarettes or were uncertain (Morean et al. 2019). Parents may be unaware of their children's vaping; in one study of parents of middle school and high school students' parents, only 44.2% of parents could identify a JUUL as a vaping device (Patel et al. 2019).

Conclusions

Adolescents are susceptible to direct pulmonary injury, addiction, and other health risks from e-cigarettes, and are unique in that most are primary users and not utilizing these products for smoking cessation. The increasing rates of nicotine dependence are highly concerning, as teens are prime suspects for new nicotine addiction that increases the threat of cigarette smoking. Historically, most long-term smokers are committed smokers by the age of 18 years old, and users have significant difficulty quitting once they have developed nicotine dependence (Zhu et al. 2000). The companies that manufacture and sell e-cigarettes directly targeted adolescents through sophisticated and well-developed marketing strategies. Preventing primary use in teens and young adults is the most important step that can be taken to reduce the long-term complications of nicotine exposure. In order to reduce the effects of this epidemic of adolescent vaping, it is essential to support efforts to decrease the initiation of nicotine and THC use among adolescents including regulations that restrict advertising directed toward adolescents, eliminate flavored vaping liquids, and banning e-cigarette sales to youth. Further study is also needed to determine the long-term safety of products used on the market for the purpose of combustible cigarette smoking cessation, and available smoking cessation e-cigarette products should be sold only to adults as a minority of adolescents are actually using e-cigarettes for that purpose. We also look forward to ongoing studies of the toxicity of individual components of

e-cigarettes regarding short and long-term pulmonary effects. We urgently call for appropriate restrictions on the contents as more information becomes available about the toxicology and negative pulmonary and extrapulmonary effects.

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Declaration of interest

The primary employment of the authors is shown on the cover page. The review, including conception, drafting, and final conclusions, is the work of the authors, and the views are not necessarily those of their employers. Dr Casey has testified regarding electronic cigarettes during the 2019 EVALI outbreak in Massachusetts State proceedings, including to the governor and attorney general. The other authors have not appeared in any legal/regulatory proceedings. The authors were not compensated for the drafting of this manuscript. The authors do not have any financial conflicts of interest regarding this manuscript to report.

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