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REVIEW ARTICLE

Electronic Cigarettes and Vaping in Adolescents: State-of-the-Art

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ABSTRACT

Electronic cigarettes (EC) constitute a subset of electronic nicotine delivery systems (ENDS), designed to mimic conventional cigarettes (CC). These devices heat a liquid solution containing flavors, nicotine, or tetrahydrocannabinol to generate an aerosol that is inhaled, garnering significant interest among adolescents from early ages, accompanied by an increased incidence of usage and a lack of awareness regarding their effects, fueled by advertising campaigns portraying EC as innocuous. EC induce pulmonary, gastrointestinal, cardiovascular, neurological, cutaneous, and other complications, ranging from mild to fatal. The emergence of electronic cigarette or vaping product use-associated lung injury (EVALI) was first reported in 2017, with a subsequent surge in cases prompting numerous alerts in the United States. Despite public health measures restricting the sale of specific EC or vaping products in certain countries, adolescent consumption remains inadequately controlled. It is imperative for pediatricians and primary care physicians to understand the implications of vaping, facilitating timely preventive and therapeutic interventions.

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Cigarrillos Electrónicos y *vaping* en adolescentes: estado del arte

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RESUMEN

Los cigarrillos electrónicos (CE) hacen parte de los sistemas electrónicos dispensadores de nicotina (ENDS, por la sigla en inglés de *electronic nicotine delivery systems*), fabricados con características que simulan los cigarrillos convencionales (CC). Estos dispositivos calientan una solución líquida con sabores, nicotina o tetrahidrocanabinol para crear un aerosol, que se inhala; esto ha generado gran interés entre adolescentes desde edades muy tempranas, con aumento en la incidencia del consumo y desconocimiento de sus efectos, por campañas publicitarias que muestran los CE como inocuos.

Los CE generan compromiso pulmonar, gastrointestinal, cardiovascular, neurológico, tegumentario, entre otros; con diferentes grados de afección desde leves hasta la muerte.

La enfermedad pulmonar asociada al CE o productos del vapeo (EVALI, por sus siglas en inglés) se empezó a reportar desde el año 2017, y el aumento de casos de EVALI en Estados Unidos generó la emisión de numerosos avisos. Desde salud pública se han generado restricciones en algunos países sobre la venta de ciertos tipos de productos de CE o vapeo, sin lograr controlar el consumo entre los adolescentes.

Para el pediatra o el médico de atención primaria es indispensable conocer las implicaciones de vapeo, para realizar acciones de prevención y tratamiento oportunos.

METHODOLOGY

The information presented in this review was extracted following a search conducted between August and November 2022 in the databases PubMed, ClinicalKey, ScienceDirect, SciELO, and LILACS. MeSH terms used were "Electronic cigarettes," "Electronic Nicotine Delivery Systems," "Vaping," "Asthma," "Lung Injury," and "Adolescent." Articles published in English and Spanish were included with no publication date limitation, encompassing a range of methodological designs including case series, controlled clinical trials, meta-analyses, systematic reviews, and observational studies. Priority was given to studies focusing on populations of electronic cigarette (EC) users under 18 years of age. Criteria for exclusion were non-availability of the full text and languages other than English and Spanish. Initially, 232 articles were identified. The review of titles and abstracts was conducted by three evaluators. Subsequently, 182 articles were excluded due to reasons such as unavailability of the full text, language other than English or Spanish, duplication, or differing methodological design from those mentioned. This resulted in a total of 50 articles being selected for analysis.

OVERVIEW

Electronic cigarettes (EC) are battery-operated devices that heat a liquid to produce an aerosol, which the user inhales through a mouthpiece. Also known as "E-cigs" or "Pods," the act of using EC by inhaling the aerosol (incorrectly called vapor) generated from the device is referred to as "vaping." The liquid added to EC is known as "E-juice," (1-2).

In 2003, the World Health Organization (WHO) approved the Framework Convention on Tobacco Control, comprising measures to reduce tobacco supply and demand through price increases, regulation, and education. In the same year, the first commercially successful EC was created in Beijing by Hon Lik. EC were introduced in Europe and the United States in 2006 (1).

Research and regulation of EC are challenging due to the diversity and rapid changes in nomenclature, design, technology, and the variety of liquids used. Most EC share similar design features, consisting of three essential components: a battery, a heating element, and a liquid reservoir. Upon inhalation by the user, negative pressure closes a switch, activating the heater that converts part of the liquid into an aerosol for inhalation (3).

EC are classified into several ways, one of the most practical classifications divides them into four generations. First-generation EC, or cig-a-likes, designed to resemble conventional cigarettes, are disposable, easy to use, and ultra-portable but have short battery life and low liquid capacity. Second-generation vape pens have longer-lasting rechargeable batteries and larger pre-filled or refillable tanks. Third-generation devices offer more power and customization features, with lower resistance for quicker heating. Fourth-generation pod mods use pre-filled or refillable cartridges with nicotine salts, allowing for high nicotine concentration delivery; they are user-friendly and less recognizable as EC (4).

EC contain numerous components, some constant like humectants and others variable like flavorings and nicotine.

- Humectants: Propylene glycol and glycerin, used as solvent vehicles to generate aerosols, can cause acute toxicity, dermal irritation, and respiratory tract irritation. While not toxic at room temperature, upon heating, they form thermal degradation products like volatile organic compounds and carcinogens like formaldehyde, acetaldehyde, and acrolein (5).
- Metals: Chromium, nickel, selenium, aluminum, iron, and lead, originating from the heating coil or other parts like wires or batteries (5).

- Flavorings/Aromatics: Over 7000 have been described, generally recognized as safe for ingestion. However, they can induce inhalation toxicity as they form aldehydes and other respiratory irritants when heated (1,4).
- Nicotine: A highly addictive chemical that reaches the brain within 15 seconds after inhalation, creating immediate pleasurable effects. It activates the sympathetic nervous system and is thought to be associated with the risk of myocardial ischemia, arrhythmias, cardiac tissue remodeling, thrombogenesis, and endothelial dysfunction. The extent of exposure varies based on device characteristics, liquids, and usage methods. For instance, 3 ml of e-liquid at a concentration of 6 mg/ml nicotine equates to the nicotine in 20 cigarettes. Devices like JUUL use nicotine salts, created by adding acid to reduce pH and increase bioavailability, containing over 50 mg/ml of nicotine (1,4-5).
- Tetrahydrocannabinol (THC): Can be added as vaporizable cannabis oil. Due to its viscosity, some suppliers use vitamin E acetate as a diluent, which has been linked to hyperreactivity of the respiratory tract, lung inflammation, and lung injury associated with EC or vaping (EVALI).

Regarding the accuracy of nicotine content labeling on e-liquid containers, a study by Buettner-Schmidt et al. (6) found that 51% of labels in e-juice containers from 16 stores did not accurately reflect the nicotine levels in the products. In one case, actual levels were 172% higher than indicated on the label. 43% of e-juice containers claiming to be nicotine-free contained up to 0.48 mg/ml, and 65% of the containers were not childproof, posing a risk of easy ingestion.

Who Uses Electronic Cigarettes and Why?

In the systematic review and meta-analysis by Yoong et al. (7), which included the most recent prevalence data from 26 national surveys across 69 countries involving 3925 children and adolescents (aged 8–19 years), the pooled prevalence for ever using EC was found to be 17%, and 8% for current use. The rate was higher in high-income geographical regions; in Colombia, the prevalence was estimated at 15% in the 13 to 15-year-old group (7).

Reports from the Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) in the United States showed a more than threefold increase in the use of tobacco products among high school students between 2017 to 2019 (from 3% to 10.5%) and more than twofold in senior high students (from 12% to 27.5%), with the majority of these students consuming nicotine in the form of EC (8).

The Monitoring the Future Survey on Substance Use reported a significant increase in EC use in 2018, with 25% of 12th graders and 20% of 10th graders participating. This represents the largest increase for any substance recorded by the survey in its 44-year history (3).

In adults, conventional cigarettes (CC) are still the most used tobacco product, as evidenced by the 2017 national health survey, where current EC use in adults was 3%, while CC use was 14%. Among those over 18 years, the highest EC usage was among young adults aged 18 to 24 years, with 5% being users (3).

In Colombia, two studies assessed the consumption of nicotine delivery systems (SEAN): the Third Andean Epidemiological Study on Drug Use in the University Population and the 2017 National Youth Tobacco Survey. These studies showed that in 2016, the prevalence of participants having

ever used EC was 16%. Colombia ranks second in the consumption of these products after Ecuador. 51% of schoolchildren have heard about the existence of EC, 15% of schoolchildren reported having experience with EC use, especially in urban areas and private schools, and 14% of students in Colombia believe these products are less harmful than CC (9).

Regarding the reasons why young people use EC, a study by Evans-Polce et al. (10) involving 7677 12th-grade students, of which 2664 (35%) had used EC, found that the main reasons for use were to "experiment" (55%), for the flavor (37%), out of "boredom" (22%), and to have a "good time" (20%), among others. Only 8.5% of adolescents used EC as a strategy to quit CC. These findings were reinforced by a systematic review of six studies among young adults aged 18 to 25 years in various settings (United States, Romania, France, New Zealand, and Saudi Arabia) (11), where curiosity and use by friends were the main reasons for starting EC use.

Young people are often unaware of the ingredients in their EC; 66% believe they contain only "flavors," and 31% report that flavors are the main reason for their use, possibly because flavors reduce the irritation experienced when inhaling the aerosol. Additionally, the industry targets adolescents with colorful packaging and popular appealing flavors (12,13). Although the 2009 Family Smoking Prevention and Tobacco Control Act banned flavors (except menthol) in cigarettes, the tobacco industry has a history of using flavors to deliberately attract adolescents to their products. Therefore, due to the great appeal of flavored EC to young people, the policy of the American Academy of Pediatrics (AAP) recommends that the FDA ban all flavors, including menthol (14).

Moreover, young people are frequently exposed to misleading advertising about these products. In the systematic review by Collins et al. (15), 124 publications on EC marketing and communication were evaluated, showing that, compared to CC, EC were presented as healthier, less expensive, more socially acceptable, unrestricted by smoke-free policies, and more environmentally friendly. Additionally, they used "youth appeals" in advertisements, such as the depiction of EC use by celebrities. Likewise, more than 40% of online vendors use promotional codes, loyalty programs, and discounts for referring new customers. Information about EC was widely available on social media, and most communications were in a positive or neutral tone, promoting their use. The CDC reports that 4 out of 5 high school and senior high students (over 20 million) are exposed to advertisements, 68% in stores, 41% on the internet, 38% on television, and 24% in newspapers or magazines (16).

What Are the Health Risks?

Effects on multiple organs have been described (Table 1) (1,3,17-18). Even the genetic and epigenetic impact on the pulmonary system from the various chemical components derived from EC use has been reported. Exposure to these aerosols is associated with oxidative and alkylating damage to DNA (19). It also causes alterations in the transcriptome, such as the reduction of gene expression related to the immune system and the increase in gene expression involved in the oxidative stress response. In murine models, it has been demonstrated that there are not only maternal health effects but also fetal health implications (19).

Table 1. Described Effects of Electronic Cigarette Use on Various Organs

Pulmonary	• Airway irritation, increased mucus hypersecretion, exacerbated respiratory symptoms in patients with asthma, cystic fibrosis • Bronchial damage • Decreased lung capacity (FEV1) • Bronchiolitis obliterans • Pulmonary fibrosis • Pneumonitis, including lipid, eosinophilic due to hypersensitivity, and interstitial • Pneumothorax • EVALI (E-cigarette or Vaping product use-Associated Lung Injury)
Cardiovascular	• Increase in diastolic blood pressure • Arrhythmias • Decreased overall ventricular performance • Coronary vasoconstriction
Central Nervous System	• Seizures • Circadian rhythm disturbances • Decreased psychomotor functioning • Mental health issues
Immune System	• Proinflammatory response in epithelial cells and pulmonary fibroblasts • Decreased survival in epithelial cell lines, dysregulation of gene expression, loss of pulmonary endothelial barrier • Increased susceptibility to infections
Oral Cavity	• Dental fractures • Pulp necrosis • Caries • Oropharyngeal cancer
Skin	• Burns from battery explosion
Gastrointestinal Tract	• Nausea • Vomiting • Nicotine: Pancreatic cancer
Pregnancy	• Premature birth • Neonatal apnea

Source: Created based on (1,3,17)

In relation to the airway, Staud et al. (20) evaluated 10 non-smokers before and after 20 inhalations of EC, one group with nicotine and another without. The study demonstrated an alteration in pulmonary homeostasis, indicated by altered transcriptomes of small airway epithelium and alveolar macrophages, and elevated levels of endothelial microparticles in plasma in the nicotine group, reflecting endothelial cell injury. Reidel et al. (21) analyzed sputum samples from CC smokers, EC users, and non-smokers using quantitative proteomics. The results showed that EC use alters the protein profile of innate defenses in respiratory secretions and induces changes similar to those related to smoking.

In 2019, the United States experienced an outbreak of e-cigarette or vaping use-associated lung injury (EVALI), a term coined by the CDC. Dozens of deaths and thousands of cases of acute respiratory compromise due to nonspecific injuries occurred. This outbreak was more closely associated with the vaping of cannabis derivatives containing vitamin E acetate, which was found in most of the bronchoalveolar lavage (BAL) samples. However, other pathogenic components likely

also contributed (22). In the first case series described by Layden et al. (22), 98 patients presented respiratory symptoms such as dyspnea, cough, pleuritic chest pain, and hemoptysis, constitutional symptoms like fever and chills, and gastrointestinal symptoms like nausea, vomiting, diarrhea, and abdominal pain. Additionally, physical examinations found tachycardia, tachypnea, fever, and hypoxemia, often progressing to respiratory failure. From this case series, the criteria for confirmed EVALI cases emerged (Table 2). The imaging alterations described in chest computed tomography scans of these patients are varied, with the most frequent pattern being centrilobular nodules and ground-glass opacities with subpleural preservation (23).

Table 2. EVALI Criteria

Confirmed Case
• Use of an electronic cigarette ("vaping") or "dabbing" within the previous 90 days*
• Pulmonary opacities on chest radiography or computed tomography

• Exclusion of pulmonary infection based on:
  • Negative PCR or rapid influenza test
  • Negative respiratory viral panel
  • Negative tests for clinically indicated respiratory infections (e.g., urine antigens for Legionella pneumophila and Streptococcus pneumoniae, blood cultures, sputum cultures, BAL if performed)
  • Negative tests for HIV-related opportunistic respiratory infections (if applicable)

• Absence of a plausible alternative diagnosis (e.g., cardiac, neoplastic, rheumatologic)

Source: Created based on (22)

Vitamin E acetate has been proposed as a causative agent of these injuries, based on evidence from studies like that of Blount et al. (24), where BAL samples from 51 patients with EVALI and 99 healthy participants were analyzed. Vitamin E acetate was identified in 94% of BAL samples from EVALI patients vs. 0% from the comparison group. THC or its metabolites were detected in 47 of 50 BAL samples (94%) from individuals who reported vaping THC products in the 90 days prior to the onset of the illness. However, the role of nicotine or its metabolites, detected in 30 of 47 samples obtained (64%), cannot be dismissed. The role of vitamin E acetate has also been described in murine models (25), where vitamin E acetate in aerosol form causes pulmonary edema depending on the dose, increased permeability of the alveolocapillary barrier to proteins, and an inflammatory pattern with abundant multinucleated, lipid-laden macrophages.

The association between EC use and asthma has been studied (26, 27). In animal models, an increase in bronchial hyperreactivity has been observed, with a significant increase in airway inflammation dominated by Th2, higher production of IL-4, IL-5, and IL-13, and greater eosinophil infiltration, reflected in increased mucus production and the thickening of airway walls (28,29). An increased risk of respiratory infections has been reported due to impaired ciliary function, reduced cough receptor sensitivity, impaired neutrophil and alveolar macrophage function, and altered expression of genes and molecules involved in immune reactions (30,31).

In adolescents, EC use increases the likelihood of an asthma diagnosis, being an independent risk factor after controlling for various covariates (32,33). This finding was reinforced by Li et al. (27) in a meta-analysis of 10 cross-sectional studies with a population of 483,984 high school students averaging 15–16 years, where the median prevalence of EC use was 11%, and a significant association with higher odds of having asthma was found. Additionally, it has been shown that EC-using adolescents have a higher risk of school absenteeism due to asthma (34) and that asthmatic adolescents

are more likely to report an asthma attack in the previous year when exposed to second-hand EC (35). Also, the relationship between EVALI and asthma has been studied, finding that between 30%–44% of adolescents hospitalized with EVALI were asthmatic, and asthma is a factor associated with more severe outcomes and mortality (23% of fatal cases had a history of asthma) (36,37).

In the cardiovascular system, evidence of acute hemodynamic changes in vascular (increased arterial stiffness, blood pressure, and sympathetic tone) and cardiac function (increased myocardial fibrosis and coronary disease, with reduced myocardial blood flow and nitric oxide production) has been observed. Many of these vascular effects seem to be attributable to nicotine exposure. Evidence suggests that the acute cardiovascular effects of EC can accumulate over time with prolonged use, leading to long-term cardiovascular diseases (38).

In the nervous system, EC use has been associated with seizures (39). Faulcon et al. (40) reported 114 cases of seizures in EC users with nicotine reported to the FDA between 2010–2019. 85% reported that the seizures occurred within 24 hours of last use, and 62% within 30 minutes of last use. Chronic EC use with nicotine has been shown to alter the homeostasis of various neurotransmitters in mesocorticolimbic areas, especially in the frontal cortex and striatum, which can lead to the development of dependence (41).

EC use has also been associated with mental health issues in adolescents. In the systematic review by Becker et al. (42), a higher risk of depression, anxiety, suicidal ideation, suicide attempts, eating disorders, attention deficit hyperactivity disorder, and conduct and delinquency disorders in adolescents was found.

Exposure to EC has also been linked to increased risk of deterioration in periodontal, dental, and gingival health, as well as changes in the oral microbiome. Case reports have described extensive dental damage as a result of EC explosions (43).

Liquid nicotine poisoning, especially in young children due to accidental ingestion, is another risk described. The most frequent symptoms are vomiting, salivation, nervous appearance, truncal ataxia, and respiratory difficulty. The lethal dose of nicotine in adults is between 30–60 mg, while in children it is approximately 0.5 mg/kg, representing a significant risk given that EC liquid can contain between 6 and 36 mg/ml of nicotine and each cartridge contains up to 50 ml (3,44).

Relationship With the Use of Other Substances

Nicotine affects neural pathways underlying pleasure and reward and can increase the brain's sensitivity to other psychoactive substances and drug-seeking behaviors. In the study by Silveira et al. (45), 11,996 youth aged 12–17 years were followed for 10–13 months. It was found that past use of EC predicted subsequent use of any drug, including alcohol, marijuana, and amphetamines.

There is concern that these consumers may have an increased the risk of CC use, potentially undoing decades of progress in reducing tobacco consumption (1). In the meta-analysis by Soneji et al. (46) of 9 longitudinal studies (n = 17,389) of youths with no prior CC experience, it was found that EC use was significantly associated with subsequent CC use, even when known demographic and behavioral risk factors for CC use were controlled. Chaffe et al. (47) found that among youths who had already experimented with CC, EC use was associated with progression to current established smoking, suggesting that in youth who begin using CC, EC may increase, rather than decrease, the risk of sustained CC use. Baenziger et al. (48), in their meta-analysis of 25 studies of non-smokers from age 10, found a higher risk of CC consumption with exposure to EC, for those who had never smoked, and among ex-smokers, a higher risk of relapse into smoking was observed.

Role of the Physician

The American Academy of Pediatrics (AAP) recommends implementing screening actions for the use and exposure to EC starting at age 11 as well as providing prevention counseling. This includes advising that all places where children spend time should be free of tobacco and EC use, not recommending EC as a product for smoking cessation, and supporting adolescents in their attempts to quit smoking. The 5A model for screening and counseling on tobacco use has been adapted for adolescents who use EC (Table 3) (1,49). In Table 4, a series of questions for assessing EC use in adolescents and considerations to take are proposed (1).

Table 3. Modified 5A Model for Screening and Counseling on EC Use in Adolescents

Ask	Inquire all patients about their use
Advise	Provide clear, strong, and personalized advice to quit
Assess	Ask if the patients is willing to stop using EC
Assist	Help in quitting
Arrange	Schedule follow-up

Source: Created based on (1,49,50)

Table 4. Guiding Questions to Assess EC Use in Adolescents

To everyone over 11 years old: Have you ever used an electronic cigarette?	
Questions	**Considerations**
What type of device do you use?	• Higher battery voltages increase the risk of chemical reactions creating toxic products.
What substances have you vaped?	• **Flavoring:** Increases both the risk of continued use and misconceptions about safety. • **Nicotine:** Higher concentrations have been associated with more intense daily EC use and increased CC use. • **Cannabis derivatives and other substances:** Increase the risk of dependence on alternative substances, EVALI, and other problems.
At what age did you start vaping?	• A younger age of initiation poses a greater vulnerability to addiction.
Have you had any problems at school, with parents, or with the police because of vaping?	• Vaping in adolescence has been associated with delinquency, suspension or expulsion from school, and increased family conflicts.
Have you experienced symptoms of dependence: difficulties in reducing use or developing withdrawal symptoms when you couldn't vape?	• Dependence indicates the need for closer monitoring and consideration of pharmacological interventions.
Do you use other substances?	• Vaping is a risk factor for the use of other substances.
Do your friends and family members vape?	• Peer vaping is a common entry point and a factor that perpetuates vaping.

Source: Created based on (1)

Specific clinical interventions for vaping are still underdeveloped, so general principles and established treatments for conventional cigarette (CC) use have been applied. It is important to assist young individuals in maintaining a usage log and encourage them to allow family participation (e.g., restricting access to vaping devices, supporting adherence to behavioral goals, and positively reinforcing change). Likewise, parents who smoke should be referred to smoking cessation resources. Individual or group cognitive-behavioral therapy for nicotine use can help young people manage symptoms and prevent relapses with good effectiveness in cessation rates and should be evaluated by a toxicologist (1).

CONCLUSIONS

The use of electronic cigarettes is not a harmless practice. It has been associated with harmful effects on multiple systems, as well as with the use of other substances and an increased likelihood of using conventional cigarettes in adolescents. To date, there is no evidence to validate the use of these devices as strategies for smoking cessation. The pediatrician plays a fundamental role in accompanying adolescents. It is recommended to ask everyone over the age of 11 about the use of such devices, to advise, and to support the process of cessation.

CONFLICT OF INTERESTS

We declare that there are no conflicts of interest.

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