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Clinical manifestations of EVALI in adolescents and the impact of e-cigarettes on the respiratory diseases

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ABSTRACT

Introduction: In recent years there has been a significant increase in the popularity of electronic cigarettes among adolescents and young adults worldwide. E-cigarettes have reached the market without the extensive preclinical toxicology testing or long-term safety studies required for conventional therapeutics and medical devices. Their effectiveness as a smoking cessation intervention, their impact at the population level and whether they are less harmful than combustible tobacco products are highly controversial. Studies show measurable adverse biological effects on organ and cell health in humans, animals and in vitro. E-cigarette use also increases the risk of respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma. There is a serious risk of complications associated with e-cigarette use, such as EVALI (E-cigarette or Vaping Product Use-Associated Lung Injury) - serious lung damage associated with, especially for adolescents. This paper reviews the effects of e-cigarettes on respiratory health.

Purpose: The purpose of this scientific paper is to review the current knowledge of the effects of using e-cigarettes on the development of respiratory diseases.

Review Methods: We conducted our study as a literature review based on information gathered from PubMed, Embase, GoogleScholar using combinations of the following keywords: e-cigarettes, vaping, chronic obstructive pulmonary disease, asthma, EVALI.

The state of knowledge: Current research suggests that e-cigarettes may have negative effects on respiratory health. Chemical ingredients in e-cigarette liquids and aerosols can cause tissue damage. Substances such as propylene glycol, vegetable glycerin and flavourings can irritate the mucous membranes of the airways, which can lead to inflammation in the lungs. The nitrosamines contained in e-cigarettes are carcinogenic. Their long-term inhalation may increase the risk of developing cancer. The use of e-cigarettes increases the risk of respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma. One of the dangerous complications associated with e-cigarette use is EVALI, or E-cigarette or Vaping Product Use-Associated Lung Injury. This is a serious lung injury associated with the use of e-cigarettes or other inhaled products. Young people, especially those who use e-cigarettes containing psychoactive substances, are at higher risk of EVALI. More research is needed to fully understand the mechanisms and effects of e-cigarette use.

Conclusion: Our literature review suggests a potential impact of e-cigarette use on the development of respiratory disease. Despite the existing evidence of negative effects of e-cigarettes on respiratory health, more research is needed to better understand the mechanisms of action and the long-term effects of using these devices.

Keywords: E-cigarettes; vaping; chronic obstructive pulmonary disease; asthma; EVALI

INTRODUCTION

An electronic cigarette (e-cigarette), commonly known as a vaping device, is a nicotine delivery system that utilises non-combustible tobacco products. E-cigarettes produce a nearly odourless vapour by heating and aerosolizing nicotine, vegetable glycerin (VG) and propylene glycol (PG), which is inhaled [1,2]. Electronic cigarettes were introduced as smoking cessation aid and safer alternatives to traditional cigarettes, and although the health effects of their use remain uncertain, subsequent studies have shown their negative impact on various aspects of health including respiratory health [3]. Throughout 2019 there was a significant increase in lung injuries related to the use of e-cigarettes, known as e-cigarette or vaping product use-associated lung injury (EVALI), highlighting the concerning health risks associated with these products, which unfortunately led to fatalities among many patients [2]. Data on the relationship between e-cigarette use and respiratory diseases such as COPD and asthma are limited, yet existing studies suggest the correlation [3]. Some studies indicate improvements in health outcomes for patients with COPD who stopped smoking or reduced cigarette intake by switching to vaping [4]. The prevalence of e-cigarette exposure in the general population is rising, especially among adolescents [5,6]. According to the World Health Organization in 2011 there were 7 million EC users and by 2018 this increased by about 5.9 times (41 million) [7]. A study by Gallus et al. indicates that 8.3 million people in European countries might be currently using electronic cigarettes [8]. The respiratory effects of combustible tobacco use have been extensively documented, whereas the impact of using electronic cigarettes on respiration remains largely unexplored [9]. Clinical practitioners and researchers have increasingly directed their attention to respiratory symptoms associated with lung injury and COPD related to electronic cigarette use [10, 11]. Epidemiological studies conducted among young adults have revealed a significant link between electronic cigarette use and the presence of respiratory symptoms, as well as COPD [12,13]. However, the long-term health effects of electronic cigarette use are rarely available, as the evidence provided is limited to cross-sectional data or short-term studies. Our study addresses the concern of the detrimental effects of electronic cigarette use on respiratory health.

REVIEW METHODS

We conducted our study as a literature review based on information gathered from PubMed, Embase, Google Scholar and explored the latest effects of e-cigarettes on the respiratory system.

THE STATE OF KNOWLEDGE

Recent studies suggest that e-cigarettes may have a negative impact on respiratory health. Chemical components found in e-liquid and aerosols can inflict harm on tissues. Ingredients like propylene glycol, vegetable glycerin, and flavorings may provoke irritation to the mucous membranes in air passages, prompting lung inflammation [1]. Moreover, the presence of nitrosamines in e-cigarettes poses carcinogenic risks, potentially elevating the likelihood of cancer over prolonged inhalation [2]. E-cigarette use also increases susceptibility to respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma [10]. In particular, a dangerous complication associated with e-cigarette use is EVALI, or E-cigarette or Vaping Product Use-Associated Lung Injury, which is a severe lung injury associated with the use of e-cigarettes or other inhaled products [10]. Adolescents, especially those who use e-cigarettes containing psychoactive substances, are at increased risk of EVALI.

Components of e-cigarette liquid and their effects on the lungs

E-cigarettes are battery-operated devices that deliver nicotine, flavourings, and other constituents to the user by heating flavoured e-cigarette liquid (e-liquid) solutions to temperatures sufficient to form aerosols. There are currently over 7,000 different e-liquids that are commercially available [14]. The main components that are consistently found, in varying concentrations, in e-liquid are water, propylene glycol, glycerol, glycerin, andnicotine [15,16]. Components described in e-cigarette fluid and aerosol.(table 1)[16].

Aerosol	**E-liquid**
E-liquid components	Glycols (propylene glycol, glicerol)
Carbonyls(formaldehyde, acrolein, propionic aldehyde)	Nicotine
nanoparticles	Tabacco-specifin nitrosoamines
Volatile organic compounds(benzene, styrene, toluene	Flavorings(cinnamaldehyde, diacetyl, 2,3-pentanedione, acetoin, maltol, pulegone
Metal particles (copper, lead, cadmium chromium, cadmium, aluminum, tin)	Phenols

Table 1. Components of e-cigarette.

Aldehyde components such as acetaldehyde, formaldehyde, and acrolein are amongst the most harmful substances in tobacco smoke and also in e-cigarette vape [17]. Acrolein is a known respiratory toxicant produced by conventional cigarettes and has been shown to be associated with the development of COPD [16,18]. A recent study has shown that e-cigarettes produce acrolein at a similar level as produced by conventional cigarettes [18]. Exposure of airway epithelial cells to e-cigarette vapour induces dysfunction in ion channels, resulting from acrolein-dependent modification of the ion channel protein [19]. Furthermore, propylene glycol is not present in conventional cigarettes. One study found out that exposure to an aerosolized mixture of propylene glycol and glycerol reduced cell membrane fluidity and impaired protein diffusion in human bronchial epithelial cells, suggesting impaired cell function [20,21]. In addition, some of the flavouring chemicals have been reported to be harmful to lung cells including: cinnamaldehyde, diacetyl, 2,3-pentanedione, acetoin, maltol and pulegone [22,23,24]. Cinnamaldehyde is the main chemical in cinnamon-flavoured e-cigarettes and has been shown to inhibit respiratory immune cell function and impair epithelial barrier function in human bronchial epithelial cells [22,23]. Butter flavouring and acetoin has been reported to strongly induce a pro-inflammatory response (through induction of IL-8 release) and inhibit epithelial barrier function in human bronchial epithelial cells [22]. The heating element within an e-cigarette is the largest potential source of toxic metal exposure. E-cigarettes aerosols may contain heavy metals such as copper, lead and cadmium, which are known to cause respiratory distress. It has been reported that heavy metal particles in e-cigarette vape - copper nanoparticles can alter mitochondrial reactive oxygen species (mtROS) and the stability of the electron transport chain complex (ETC) resulting in mitochondrial DNA damage and therefore lead to mitochondrial dysfunction in lung fibroblasts [25]. Nicotine is a highly addictive substance that can be a component of an E-cigarette. Nicotinic acetylcholine receptors (nAChR) activation increases cytosolic Ca2+ levels and can inhibit CFTR in airway epithelium [27,28,29]. Nicotine can affect alveolar macrophages [30]. Nicotinic acetylcholine receptors can regulate cell proliferation and inhibit apoptosis and uncontrolled cell proliferation is a hallmark of cancer [31]. Thus, e-cigarette use may affect inflammation in the airways that could alter susceptibility to infection and increase the risk of developing COPD, lung cancer or asthma exacerbations [1].

Electronic cigarette or vaping product use-associated lung injury EVALI

Electronic cigarette or vaping product use-associated lung injury is a respiratory illness, typically of an acute or subacute onset, characterised by a range of clinicopathologic findings that resemble those seen in various pulmonary diseases [32]. The EVALI outbreak in the USA in 2019 heightened public health concerns regarding the risks associated with vaping, particularly among young people. EVALI patients commonly present with nonspecific clinical symptoms resembling viral infection, including respiratory, gastrointestinal and constitutional symptoms. Suggested diagnostic criteria of EVALI (table 2).

Suggested Diagnostic Criteria of EVALI
Symptoms (fever, cough, dyspnea)
Vaping history in past 90 days
Laboratory work (leukocytosis, transaminitis, elevated ESR/CRP)
Suggestive imaging
Exclusion of infention - everyone
Exclusion of cardiac, rheumatologic, and oncologic causes – case by case
Bronchoscopy with BAL- case by case
Lung biopsy – case by case

Table 2. Suggested diagnostic criteria of EVALI .

When detected in the early stages, many patients with EVALI show improvement and return to their baseline condition with cessation of vaping, supportive measures and glucocorticoid therapy [33,34,35]. However, some patients experience a more progressive course, potentially leading to death from respiratory failure. Survivors of such cases may develop severe pulmonary scarring and chronic dysfunction, sporadically necessitating lung transplantation [36]. Most reported cases of EVALI are linked to the use of THC-containing vaping products. Vitamin E acetate, detected in samples analysed by the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC), is considered a probable factor in the development of EVALI. Upon inhalation vitamin E acetate is assimilated into the inherent surfactant-forming phospholipids, leading to heightened permeability and diminished functionality [33,37]. Another possible negative consequence of vitamin E acetate is linked to its decomposition when exposed to heat, which results in the formation of reactive compounds [38,39]. A study by Abdallah B et. al described clinical manifestation of EVALI in adolescents. A total of 41 adolescents were included for this study. Constitutional symptoms were the most common presenting symptoms, followed by gastrointestinal and

respiratory symptoms. The most common constitutional symptoms were fever and fatigue or malaise. The most common gastrointestinal symptoms were vomiting followed by nausea. Shortness of breath and cough were the most common respiratory symptoms. Chest CT scan showed diffuse bilateral ground-glass opacities with increased prominence in the lung bases and subpleural sparing. Systemic corticosteroids were administered during hospitalisation in 93% of patients. Clinical improvement within 24 hours of corticosteroid initiation was documented in 79% of patients [34].Following the outbreak in 2019, the incidence of EVALI cases has decreased. This decline is likely due to several factors including: heightened public awareness of the risks associated with THC-containing e-cigarettes, the removal of vitamin E acetate from certain products and increased law enforcement efforts targeting illicit products. Additionally, the FDA has expanded its Premarket Tobacco Product Application (PMTA) to encompass e-cigarette and vaping products, ensuring standardised regulation of their contents [40]. While vitamin E acetate is strongly implicated as a causative agent of EVALI, the potential involvement of other agents, such as chemicals in both THC and non-THC products, cannot be disregarded [34].

The association between electronic cigarette use and the development of COPD

Chronic obstructive pulmonary disease (COPD) is a widespread disease marked by progressive airflow limitation, pulmonary structural abnormalities and chronic respiratory symptoms including chronic cough, increased sputum production, dyspnoea and wheezing [41]. COPD is the third, after ischaemic heart disease and stroke, leading cause of death worldwide [42,43]. Cigarette smoking accounts for most cases of COPD in high-income countries. Among COPD patients, conventional smoke has been found to exacerbate mucus production, airway constriction and inflammation of the lung epithelium. These pathways also coincide with those observed in e-cigarette-induced airway epithelial dysfunction and toxicity [2,13]. Tobacco smoke is known to significantly impact children's lung development, greatly elevating the risk of COPD in their later years [42,44]. Young people who use e-cigarettes are more inclined to experiment with conventional cigarettes afterward compared to non-users. The high prevalence of e-cigarette use is expected to contribute to the initiation of cigarette smoking among teenagers, potentially predisposing them to pulmonary function impairment and COPD in adulthood. Increased mucin MUC5AC concentrations, which serves as the primary marker of mucus hypersecretion in tobacco smoking-related pathologies, among e-cigarette users were observed. Higher mucin levels are inversely associated with lung function

decline in COPD patients and serve as a biomarker of chronic bronchitis, highlighting mucins as a validated indicator of harm. The report from Reidel et al. is among the first to suggest that e-cigarette use may have deleterious effects comparable to those of conventional tobacco cigarettes [45]. Oxidative stress and inflammatory responses play pivotal roles in the development of chronic airway diseases. E-vapor exposure has been shown to lead to heightened production of reactive oxygen species (ROS) and increased secretion of the pro-inflammatory cytokines interleukin IL-6 and IL-8 in pulmonary epithelial cells, inducing observable oxidative and inflammatory responses in lung cells and tissues, which could result in unanticipated health implications [23].Activated neutrophils have the potential to exacerbate inflammatory lung diseases, including COPD. The release of neutrophil extracellular traps (NETs) represents one of the antimicrobial effects of neutrophils, which have been linked to the bronchial inflammation and structural damage observed in COPD [24,46,47]. While NET formation serves as an antibacterial immune response, it has also been demonstrated to be triggered by constituents of smoke and e-cigarette vapours, such as acrolein [45]. Clapp et al. present varied findings regarding NET formation associated with different flavourings of e-cigarettes (containing different doses of cinnamaldehyde), indicating that 1% Kola flavouring notably increases NET formation, whereas 1% Hot Cinnamon Candies flavouring significantly decreases NET formation. Anomalous NET activation could heighten NET-mediated tissue damage and respiratory dysfunction. Suppressing NET formation may facilitate increased spread of bacterial pathogens within the lungs and heighten the susceptibility to respiratory infections [24]. The disparity in findings raises concerns that flavoured e-liquids may widely contain potentially harmful chemicals and highlights the importance of investigating the respiratory effects of commonly used flavourings in e-liquid production. Dysregulated lung proteases have the potential to degrade basement membranes, leading to emphysema, as evidenced in COPD patients. Previous observations have shown elevated protease concentrations in the lungs of tobacco smokers, suggesting a causal association between smoking, increased proteolysis and lung damage. Thus, protease concentrations serve as a biomarker useful for studying the effects of vaping on the lung. Proteomic analysis of e-cigarette users' sputum has revealed heightened levels of neutrophil activation markers, including myeloperoxidase, neutrophil elastase, and proteinase-3 [45]. These findings suggest that e-cigarettes may produce similar effects on the human airways as traditional cigarettes. It is important to grasp the impacts of activated neutrophils and changes in mucin secretion dynamics on the innate immune properties of airway

secretions. Understanding the functional consequences of these alterations, to lung antibacterial and antioxidant defences and their role in chronic lung diseases like COPD, is essential.

Electronic Cigarettes use and Asthma

Asthma is a chronic inflammatory airway disease affecting 1%-18% of the population in various regions. Asthma is characterised by variable symptoms of wheeze, shortness of breath, chest tightness, cough, variable expiratory airflow limitation and life-threatening exacerbations [7]. Adult-onset asthma can be induced by different triggers, which cause inflammation leading to acute bronchoconstriction [48]. Cigarette smoke is a major trigger of asthma exacerbations, which may be one reason why some smokers made the switch to e-cigarettes. Studies have shown that while e-liquid may not contain nicotine and the same toxic chemicals found in conventional cigarettes, it still contains multiple toxins and irritants, which can lead to worsening of asthma [24]. E-cigarettes use alters the profile of innate defence genes, proteins and proteases in airway samples (nasal scrape biopsies, nasal lavage, bronchoalveolar lavage (BAL)). Among the changes seen are upregulated mechanisms such as: aldehyde-detoxification and oxidative stress, suppressed host-defence genes and elevated concentrations of pathologic mucins for instance MUC5AC and elastases including neutrophil elastase (NE) and matrix metalloproteinases (MMP)-2 and 9. As seen in COPD, increased MUC5AC levels have important implications in the pathophysiology of asthma contributing to increased airway obstruction and nonspecific airway hyperreactivity [49,50]. NE and MMPs lead to increased tissue damage and remodelling. E-cigarette users have also shown altered expression of 113 epithelial cell proteins, including the mucins MUC5AC and MUC4, suggesting the potential for impaired mucus transport - a hallmark of muco-obstructive disease [20,45]. Visual inspection of the airways during bronchoscopy reported the presence of gross physical damage to the airways themselves in e-cigarette users compared to conventional cigarette smokers and non-smokers. Asthmatics may be particularly vulnerable to e-cigarette emissions as these aerosols contain reactive chemicals that are known sensitizers and respiratory irritants. Emerging epidemiological data from the EVALI outbreak suggest a higher than expected incidence among asthmatics [51]. Asthmatics who currently smoke conventional cigarettes are often advised by their health care providers to switch to e-cigarettes as a safer alternative [52]. However, several reports now demonstrate potential adverse health effects associated with concurrent e-cigarette use in smokers. A study by Wang

et al. showed that dual users of e-cigarettes and cigarettes are more likely to report a diagnosis of asthma and are at greater risk of experiencing breathing difficulty compared with cigarette-only users [53]. The association between secondhand exposure to e-cigarette aerosol and asthma has not been widely studied. Data from the Florida Youth Tobacco Survey showed that 33% of 11- to 17-year-olds with a diagnosis of asthma had secondhand exposure to e-cigarette aerosol, which was associated with an increased risk of having an asthma attack in the previous 12 months [54]. The study by Alnajem et al. described associations between frequency of exposure to household secondhand aerosols from e-cigarettes with asthma symptoms [55]. Those who reported frequent household exposure to secondhand aerosol had the highest prevalence of current asthma and current uncontrolled asthma symptoms compared with those who did not report household exposure to secondhand aerosol. It has been suggested that second-hand e-cigarette smoking may lead to asthma exacerbations [56].

Conclusion

In this review we have provided a summary of the possible health risks associated with e-cigarettes with focus on respiratory diseases. The harmful effects of e-cigarette ingredients on the respiratory tract can be significant, especially with prolonged use. Substances such as acrolein, flavourings, nicotine, aldehydes and heavy metals can irritate the respiratory tract, increase the risk of lung inflammation and the development of respiratory diseases such as chronic obstructive pulmonary disease (COPD) and asthma. Some chemical constituents in e-cigarette liquids and aerosols, such as nitrosamines, are carcinogenic. Young people who use e-cigarettes may be at particular risk of developing respiratory diseases due to incomplete development of their respiratory system and a potentially greater propensity to experiment with different substances, and therefore require special attention from physicians. It takes decades of chronic smoking to develop lung cancer, so the effects of e-cigarette use on the population may not become apparent until the middle of this century, so it is important to continue research into the impact of e-cigarettes on lung cancer development. The use of e-cigarettes can lead to EVALI (E-cigarette or Vaping Product Use-Associated Lung Injury) and, although associated cases are relatively rare, they are potentially fatal and require the attention of general practitioners and pulmonologists. The use of e-cigarettes may be associated with various respiratory health risks and limiting or avoiding their use may help reduce the risk of developing lung disease. Despite a growing body of studies on the effects of e-cigarettes on lung disease, there are many unknown aspects and further investigation is

needed to fully understand the issue. It is important to continue research into the health effects of e-cigarettes and to take preventive measures to protect public health.

Disclosures

Author's contribution

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