

LUNG INJURY ASSOCIATED WITH THE USE OF ELECTRONIC CIGARETTES

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Abstract: INTRODUCTION: In recent years, electronic cigarettes have been used as an alternative to smoking cessation or as a substitute for conventional cigarettes. However, according to the World Health Organization, there is no scientific proof of the benefits of these practices. Electronic cigarettes are known as e-cigarettes/e-cigarettes or Electronic Nicotine Delivery Systems (ENDS), and users are popularly called vapers. They consist of a nozzle; a vaporizer or inhaler, where the user sucks in the vapor; a cartridge or atomizer, where the liquid is stored and evaporated through the rechargeable lithium battery activation mechanism; by a microelectric circuit or indicator light, activated. **METHODOLOGY:** This is a literature review, of a narrative type, which aims to describe lung injuries associated with the use of electronic cigarettes, from a theoretical point of view, through materials that have already been published on the topic in question, through analysis and interpretation of literature. The inclusion criteria were: articles in Portuguese and English; published between 2018 and 2024 and which addressed the themes proposed for this research, review-type studies made available in full. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the proposal studied and which did not meet the other inclusion criteria. **RESULTS AND DISCUSSION:** Most EVALI patients present with respiratory symptoms, including cough, chest pain, shortness of breath, and hemoptysis (Layden, JE ET AL 2020), as well as gastrointestinal symptoms, such as abdominal pain, nausea, vomiting, and diarrhea; gastrointestinal symptoms may precede respiratory symptoms in some patients (Salzman, GA ET AL 2019). Additional common symptoms include unexplained weight loss, headache, and fatigue (Layden, JE ET AL 2020), and more generally,

EVALI patients are often admitted with tachycardia, tachypnea, fever, and hypoxemia (Winnicka, L, and Shenoy, MA 2020). **FINAL CONSIDERATIONS:** As we have seen, electronic cigarettes constitute an obstacle to smoking cessation, as they encourage the renormalization of the smoking habit and cause damage to health. The evidence on such long-term harm is still inconclusive. However, the losses already reported are similar to those caused by traditional cigarettes.

Keywords: “Lung, “cigarettes”, “electronic”, “complications”.

INTRODUCTION

Lung injury associated with the use of cigarettes or vaping products (EVALI) is a serious lung disease associated with the use of electronic cigarettes or vaping products that was officially identified in 2019 during an EVALI epidemic. EVALI was primarily linked to the inclusion of vitamin E acetate (VEA) liquids, particularly e-cigarettes containing tetrahydrocannabinol (THC), largely, but not exclusively, from “informal sources such as friends, family, or in-person or online retailers. line” (Ellington S ET AL 2019). Contributing to the widespread diagnosis of EVALI in the United States has been the rapid and extensive adoption of e-cigarette use by more than 13 million individuals, including an alarming percentage of young people (25% in 2018), without federal regulation and manufacturing controls (Ghinai I, ET AL 2019). Although e-cigarettes first appeared on the U.S. market in 2007, reported EVALI diagnoses peaked in 2019. However, cases of e-cigarette-related respiratory illnesses have been documented since 2012 and continue to this day. Careful examination of factors contributing to the EVALI epidemic and identification of knowledge gaps are necessary to improve public health by preventing a similar or worse epidemic.

The use of tobacco and its derivatives causes the death of millions of people each year.

According to the World Health Organization, smoking is the most prevalent cause of preventable deaths in the world. Statistical data indicate that in 2030, if current numbers continue to grow, tobacco will cause the death of 8 million individuals per year and 80% will be in underdeveloped countries (RIGOTTI NA, 2018).

Approximately 40 billion reais were spent on medical assistance because of this practice. This represents 8.04% of all healthcare expenses. In 2009, they already showed that the global expenditure related to tobacco would result in losses of approximately US\$500 billion per year, due to consequences such as decreased productivity, illnesses and premature deaths (BARRETO IF, 2018).

Recent years have been marked by an incessant fight against smoking. Various government programs and measures are propagated with the aim of reducing or even eliminating this addiction. However, electronic cigarettes appear as an obstacle, as they contribute to the renormalization of the smoking habit. For most people, they are seen as a lesser evil and an alternative to overcoming smoking. Above all, in several countries, the advertisements behind these devices are more appealing to young people and non-smokers, with the aim of attracting new customers. Linked to this is the fascination with the innovation that these products generate in individuals, many vaporizers even have attractive features, such as controlling the music selection on other devices. Thus, this scenario facilitates the popularization of a product that causes considerable damage to health (VILARDI BMR and VILARDITMR, 2015).

This article consists of a narrative review, which aims to discuss lung injuries associated with the use of electronic cigarettes, through

considerations about them, with the aim of expanding the knowledge of students and professionals in the field about the topic in question.

METHODOLOGY

This is a literature review, of a narrative type, which aims to describe lung injury associated with the use of electronic cigarettes, from a theoretical point of view, through materials that have already been published on the topic in question, through analysis and interpretation of literature. The inclusion criteria were: articles in Portuguese and English; published between 2020 and 2024 and which addressed the themes proposed for this research, review-type studies made available in full. The exclusion criteria were: duplicate articles, available in abstract form, which did not directly address the proposal studied and which did not meet the other inclusion criteria.

The review was carried out from January 2024 to April 2024, through searches in the databases Virtual Health Library (VHL), Latin American and Caribbean Literature in Health Sciences (LILACS), National Institutes of Health's Library of Medicine (PubMed) and Scientific Electronic Library Online (SciELO). The following descriptors were used: "Lung", "cigarette", "electronic", "complications" in order to find articles relevant to the subject covered. After the selection criteria, 4 articles remained that were subjected to thorough reading for data collection. The results were presented in a descriptive way, divided into thematic categories addressing: describing the subtitles or points that were mentioned in the discussion.

DISCUSSION

In recent years, electronic cigarettes have been used as an alternative to smoking cessation or as a substitute for conventional cigarettes. However, according to the WHO, there is no scientific proof of the benefits of these practices. Electronic cigarettes are known as e-cigarettes/e-cigarettes or Electronic Nicotine Delivery Systems (ENDS), and users are popularly called vapers. They consist of a nozzle; a vaporizer or inhaler, where the user sucks in the vapor; a cartridge or atomizer, where the liquid is stored and evaporated through the rechargeable lithium battery activation mechanism; by a microelectric circuit or indicator light, activated when it is in operation (MAIA LIH and NASCIMENTO EGC, 2015).

The devices are similar to traditional cigarettes. When inhaling, using a button or suction sensor, it triggers a heating cycle until the liquid reaches the boiling point, so that it is transformed into vapor. The temperature can reach 40-65°C. Part of the vapor is released with the nicotine into the vape and the other into the environment. When exhaling, cooling occurs, and the device will only heat up again when swallowed. A cartridge can generate 10-250 jets, which can correspond, depending on the brand, to 5-30 conventional cigarettes (RIGOTTI NA, 2018).

It has been seen that liquid manufacturers do not inform their true composition, which generally contain glycerin, propylene glycol, water, flavorings and nicotine, with a variation found to be 16 to 22 mg/ml, a worrying factor due to toxicity. Furthermore, some chemical evaluations indicate the presence of potentially harmful substances in nicotine cartridges, such as formaldehyde, acrolein, acetaldehyde, heavy metals, volatile organic compounds and nitrosamines derived from tobacco. (CAVALCANTE TM, et al., 2017).

Furthermore, electronic cigarettes come in many different flavors and aromas, making them more attractive, especially to teenagers. Cartridges and refills can be found online or in tobacco stores. Flavors from current manufacturers of famous brands of conventional cigarettes are also provided. Some users use them with other substances, such as cannabis, herbs, flavorings and vodka (BALS R, et al., 2019).

In the same vein, the National Health Surveillance Agency (ANVISA) prohibited the sale, import and circulation of advertising messages of any electronic devices in Brazil. This resolution was published in 2009 and its objective was to protect consumers, as there were still no studies with concrete evidence that proved that the use of these devices was safe.

Furthermore, it is necessary to present toxicological studies and scientific tests so that ANVISA allows the use of such devices if there is any request. Despite this prohibition, it is known that the sale of ENDS is carried out clandestinely on the internet and on the streets (GRANA R, et al., 2014).

Many people think that the habit of smoking is due to the simple fact of nicotine dependence, but studies show that it involves behaviors, perceptions, sensations, pleasures and feelings, a relationship between environmental stimuli and psychosocial conditioning. In addition to physical damage, addiction to traditional cigarettes affects sociocultural values, since many individuals start smoking before the age of twenty, and socioeconomic values, since it interferes with personal expenses. Furthermore, there are several related diseases, mainly affecting the respiratory system, such as chronic obstructive pulmonary disease and worsening asthma; the cardiovascular causing atherosclerosis and stroke, the digestive developing gastroesophageal reflux, peptic ulcer and liver cirrhosis, and the genitourinary causing

erectile dysfunction and infertility (GLANTZ SA and BAREHAM DW, 2018).

Cigarette smoke contains thousands of chemical compounds, some of which are involved in the development of neoplasms. The gaseous phase of smoke contains carbon monoxide, formaldehyde, ammonia, acetaldehyde and the particulate phase contains nicotine. Combustion of the product forms several carcinogens substances such as arsenic and benzopyrene, as well as pesticide, radioactive and even rodenticide residues. (ARRUDA ITS and MENDONÇA TGL, 2019).

In addition to everything, smoking causes malignant neoplasms in the oral cavity, pharynx, esophagus, stomach and lungs. In pregnancy and the fetus, it can cause spontaneous abortion, premature placental abruption, lower birth weight and congenital malformations. It also influences other diseases, such as skin aging, melanic pigmentation, periodontal disease, halitosis, stomatitis, and a drop in immune defenses. Furthermore, the use of conventional cigarettes, according to the Tenth Revision of the International Classification of Diseases (ICD10), is a problem classified as a mental disorder and can influence the individual's behavior due to the use of the psychoactive substance (FERREIRA JMR, et al., 2015).

Scientific evidence on the long-term harm caused by electronic cigarettes is inconclusive. This scenario occurs due to the recent creation and popularization of these products. The fact that longitudinal epidemiological studies are insufficient also contributes to this unknown. Some in vitro studies have shown increased oxidative stress, apoptosis and changes in the function of cilia in the respiratory mucosa. These damages are similar to those caused by conventional cigarettes, but in a milder way. Another study in humans, 30 smokers versus controls, showed an increase in respiratory impedance and airway resistance due to acute

inhalation of vapor from electronic cigarettes (KNORST MM, et al., 2014).

On the other hand, 41 e-cigarette refill fluids were examined to evaluate cytotoxicity. Three types of cells were used as parameters: human lung fibroblasts, human embryonic stem cells and mouse neural stem cells. It was found that stem cells are more sensitive to the effects of vapors and that, as a result, concerns about pregnant women who smoke e-cigarettes have increased, due to the harmful effects on the fetus. The authors concluded that cytotoxicity was not related to nicotine, but to the number and concentration of flavors used. (KUSTERS D, et al., 2015).

User reports indicated mouth and throat irritation, coughing, headaches, dyspnea and dizziness. Studies show that exposure to vapor from e-cigarettes can cause damage to deoxyribonucleic acid (DNA) through the breakage of double strands. The results state that they are still caused in the absence of nicotine, which shows the harmful power of flavoring extracts. Double-strand breakage can bring irreparable changes and genomic aberrations. Furthermore, cell lines exposed to steam showed arrest in G1 and G2, demonstrating a change in the cell cycle profile (SILVA ALO and MOREIRA JC, 2019).

A study reveals that electronic devices can cause an accelerated heart rate and other subjective effects. Furthermore, an important point is the increased incidence of poisoning among children due to accidental ingestion of cartridges. Added to this, there is the risk of these e-cigarettes exploding while they are charging, a fact that has already caused injuries and fires. Therefore, these factors constitute additional risks to people's health and well-being (POLOSA R, et al., 2014).

LUNG INJURY

Lung Injury Associated with the Use of Electronic Cigarette or Vaping Products (EVALI) or Vaping-Associated Lung Injury (VAPI), described in 2019, is an acute or subacute respiratory disease that can be serious and life-threatening. Its pathogenesis is not yet known, but there are pathological findings of acute fibrinous pneumonitis, diffuse alveolar damage or organizing pneumonia, generally bronchiolocentric and accompanied by bronchiolitis (WEEN MP, et al., 2021).

In addition, there is acute eosinophilic pneumonia, diffuse alveolar hemorrhage, lipid pneumonia, and interstitial lung disease due to respiratory bronchiolitis, suggesting that more than one mechanism of injury may be involved. The main risk factor is the use of electronic cigarettes, but no isolated component has yet been identified that is common to all cases. Thus, the presentation of a respiratory disease without any other known factors, except a history of vaping, leaves a wide differential diagnosis (RAJAJ, et al., 2021).

At the University of Rochester Medical Center (Rochester, NY, USA), they reported 12 cases treated for suspected EVALI between June 6, 2019 and September 15, 2019. Ten (83%) patients presented with fever, dyspnea, vomiting and nine (75%) cough. 11 (92%) patients used electronic cigarette cartridges containing tetrahydrocannabinol (THC) oil, the main psychoactive component of cannabis (HAJEK P, et al., 2019).

The United States is facing an unprecedented outbreak of the disease. The Illinois Department of Public Health (IDPH) conducted an online public survey between September and October 2019 of e-cigarette users in the state. Among 4,631 survey participants, 94% reported using any nicotine-containing e-cigarette in the past 3

months; 21% with products containing THC; and 11% used both.

The prevalence of use of products containing THC was highest among respondents aged between 18 and 24 years (36%). Among the participants, 66 were EVALI patients, between the ages of 18 and 44, interviewed as part of the ongoing outbreak investigation, and were compared to the subset of 519 participants, within the same age range, who reported using THC. EVALI patients were more likely to use exclusively and frequently (more than five times a day) THC products and obtain sources informal, such as a reseller or a friend (FRIEDMANAS and TAM J, 2021).

Additionally, the US Department of Health and Human Services (CDC) in partnership with the Food and Drug Administration (FDA) surveyed 10 US states in October 2019 and observed that 86% of 867 EVALI patients reported using products with THC. in the 3 months prior to the onset of symptoms. Analyzes of product samples by the FDA and public health laboratories have identified potentially pathological constituents such as vitamin E acetate, medium-chain triglyceride oil (MCT oil) and other lipids. Vitamin E acetate can be used as an additive in vaping products and as a thickening agent in THC4 products. Therefore, these findings reinforce current recommendations not to use e-cigarette products, especially those containing THC and obtained from informal sources (WEEN MP, et al., 2021).

CLINICAL PRESENTATION

Most EVALI patients present with respiratory symptoms, including cough, chest pain, shortness of breath, and hemoptysis (Layden, JE ET AL 2020), as well as gastrointestinal symptoms, such as abdominal pain, nausea, vomiting, and diarrhea; gastrointestinal symptoms may precede respiratory symptoms in some patients

(Salzman, GA ET AL 2019).

Additional common symptoms include unexplained weight loss, headache, and fatigue (Layden, JE ET AL 2020), and more generally, EVALI patients are often admitted with tachycardia, tachypnea, fever, and hypoxemia (Winnicka, L, and Shenoy, MA 2020). Because lung biopsies are not commonly obtained in patients with EVALI, the pathological drivers of symptoms and disease progression remain poorly understood.

The respiratory system consists of two main parts: the upper and lower respiratory tracts. The upper tract includes the nose, nasal cavity, throat, and larynx. This tract is responsible for bringing air in from outside the body, through the nose and mouth.

The lower respiratory tract is divided into two zones, known as the conducting and respiratory zones. These zones encompass a total of 23 generations of airways. The conducting zone, which includes airway generations 0 to 16, is responsible for guiding inspired air towards the alveoli and humidifying it. The conducting zone begins with the trachea, which then bifurcates through 16 generations of airways to the terminal bronchioles, which conclude the conducting zone. As the airways progress in subsequent generations, their diameter gradually decreases. The airways within the conductive zone consist of thick walls of mucosa, smooth muscle, and cartilage and are lined with cilia to remove dust and foreign particles from the lung.

Clinical Presentation EVALI generally presents as an acute or subacute respiratory illness with nonspecific symptoms including shortness of breath, cough, chest pain and/or hemoptysis (Layden JE et al 2020). Most patients also present with gastrointestinal symptoms (nausea, vomiting and/or diarrhea) and/or constitutional symptoms. (fever, chills, fatigue and/or weight loss).

Symptoms develop over days to weeks. Laboratory findings are nonspecific and may include elevated white blood cell count and erythrocyte sedimentation rate. A case series observed adolescents with EVALI who experienced significant weight loss due to gastrointestinal symptoms that required hospitalization (Nacca N et al 2021). Another case series detailed the need for venovenous extracorporeal membrane oxygenation to treat EVALI in adolescents with preexisting asthma (Bradford LE et al 2020). Although the unique pathophysiology of EVALI in adolescents is not fully understood, it is reasonable to suspect a unique presentation in terms of severity, symptoms, or both. Overall, information about EVALI in adolescents is scarce and requires further investigation.

Radiological findings in EVALI are nonspecific in many cases. The most common pattern of lung injury observed with EVALI is the parenchymal organizing pneumonia (OP) pattern, observed in approximately 56% of cases, consisting of ground-glass opacity (GGO) predominant in the bilateral lower lobe or diffuse with varying degrees of consolidation (Kligerman S et al 2021). Areas of preservation of the subpleural, peribronchovascular and lobular parenchyma are common. In a smaller subset of patients, approximately 9%, EVALI will appear as diffuse, often poorly defined centrilobular nodules with little or no GGO, which may mimic excipient lung disease caused by intravenous drug use. However, in patients with excipient lung disease, centrilobular nodules are usually well defined and findings of right heart distension are common due to diffuse embolization of injected material into the pulmonary arterioles (Kligerman S et al 2021). In 20% of patients, a mixed OP pattern occurs consisting of centrilobular nodules predominant in the upper lobe with diffuse or predominant GGO in the lower lobe with areas

of mosaic attenuation. Although this pattern closely mimics hypersensitivity pneumonitis, to date, no cases of histopathologically confirmed hypersensitivity pneumonitis have been reported in EVALI.

Instead, centrilobular nodules in EVALI have been shown to pathologically represent airway-centric OP (Panse PM, et al 2020). The most severe pattern of lung injury in EVALI is a pattern of diffuse alveolar damage, comprising approximately 4% of cases. Imaging patterns consist of diffuse GGO and consolidation with volume loss and airway dilation due to alveolar collapse. Similar to other causes of diffuse alveolar damage, mortality rates have been observed in one-third of patients with this lung pattern. injury (Kligerman SJ et al 2021). Distinguishing between EVALI and COVID-19-related lung injury can be difficult. However, the presence of findings such as lymphadenopathy, centrilobular nodules, and peribronchovascular sparing, although common in EVALI, are relatively uncommon in COVID-19 lung injury, especially during the early stages of lung injury (Kligerman S et al 2021).

The histopathology of EVALI is also nonspecific. Most commonly, lung biopsies show an OP pattern (Mukhopadhyay S et al 2020), which is not surprising because most biopsies are obtained in the subacute phase of the disease. Less commonly, patterns of acute fibrinous pneumonia or patterns of diffuse alveolar damage may be found, usually in the more acute setting. or patients with more serious illnesses. To date, no specific histopathological characteristics of EVALI have been identified, but several clues may point to possible causes. Foamy macrophages are almost always present, suggesting toxic injury, and the changes are almost always distinctly bronchiolocentric (Mukhopadhyay S et al 2020).

FINAL CONSIDERATIONS

As we have seen, electronic cigarettes constitute an obstacle to smoking cessation, as they encourage the renormalization of the smoking habit and cause harm to health. The evidence on such long-term harm is still inconclusive. However, the losses already reported are similar to those caused by traditional cigarettes. Therefore, recent studies show its association with EVALI. However, the lack of technical standards and supervision over production and sale makes its use more accessible, even though it is still prohibited by A.N.V.I.S.A. (National Health Surveillance Agency). Thus, this work aimed to elucidate the consequences of using electronic cigarettes

as an alternative to traditional cigarettes. Addressing the root causes of EVALI and preventing a similar epidemic in the future will require an integrated multidisciplinary approach, including public health, clinical, and basic/translational researchers; policymakers; and e-cigarette users. These initiatives will require substantial federal investments as well as changes in regulatory policy. Improving public health and reducing the risk of another substantial disease-inducing event depends on coordinated action to better understand the inhalation toxicity of these products, informing the public about the risks of consumption, and developing and enforcing regulatory standards for products nicotine and cannabis-based inhalers.

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