

"Vaping"- a Trojan Horse Against Fight Toward Tobacco Use and Cancer: A Systematic Review of the Existing Evidence

Abstract

The purpose of this systematic review is to understand many aspects of vaping, like what is vaping, why it is more enticing to adolescents and young adults, what makes it more harmful than regular smoked tobacco products, subsequent health consequences, and what measures are currently being taken against this activity. A literature search was conducted in online database PubMed using search string "((((Lung injury*[Title/Abstract]) AND Vaping[Title/Abstract]) OR electronic nicotine delivery device[Title/Abstract]) OR electronic cigarette*[Title/Abstract]) AND e-cigarettes liquid) AND electronic cigars and search filter used were "published in the last 5 years" and "Human Studies." Similar search terms were used to search EMBASE, Web of Science, Google Scholar, and the CENTRAL database of the Cochrane Library with the help of Boolean terms. Thirty-six articles were included for a final systematic review. Many of the known brands use additives such as flavoring and thickening agents that, when used even for the short term, can cause toxicity to human lung tissues. This toxicity depends not only on the extent of the habit, but also on the variable susceptibility to lung damage, dual use with cigarettes, variability in the product design of different brands, and the liquid content used in them. Vaping may be linked with significant health issues, including respiratory diseases such as asthma, very severe forms of bronchitis such as popcorn lung, or E-cigarette, or vaping, product use-associated lung injury, and cardiovascular illnesses such as atherosclerotic plaque and myocardial ischemia. From the current systematic review, we would like to emphasize that no long-term toxicological and health studies have been carried out in humans using these vaping products and their constituents to date. Although cessation should be strongly encouraged in smokers for better quality of life, it is uncertain whether it is a universally safer option to replace cigarettes with these vaping devices.

Keywords: *Electronic nicotine delivery systems, nanoparticles, nicotine, smoking cessation, tobacco, vaping*

Introduction

The use of vaping device ("E-cigarettes") has sky-rocketed among teenagers and young adults over the past 5 years. With its high nicotine content, enticing flavors, low cost, wide availability, and distinct designs, E-cigarettes pose a severe threat to the decade long fight against tobacco use.^[1]

Over the past couple of years, there has been a rapid rise in products and liquids branded as next-generation products (NGPs) with an increase in the number of vapers attempting to use variety of these products. The aggressive marketing of NGPs as a less dangerous product than traditional smoked tobacco has resulted in the rise of these NGPs consumers around ten folds; these people are basically

individuals trying to turn from smoking to vaping, young nonsmokers, and even teens willing to experiment with tobacco-related products.^[2,3]

Vaping devices that were once marketed as safe with vapours consisting solely of water vapours are no longer considered a safer alternative to smoking.^[4,5] Research conducted by various scientists around the world has confirmed the presence of common intoxicants and carcinogens that are usually found in daily smoked cigarettes, although in small amounts.^[6,7]

In addition to the increased risk of continued use of traditional cigarettes, alcohol, opioids, and other illicit drugs, evidence suggests that E-cigarette use also exposes adolescents to several acute and long-term health hazards that outweigh potential benefits of using

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vaping devices as a smoking cessation tool in this age group.^[1]

To date, very limited scientific evidence has been available to support the safety of E-cigarette or the effectiveness of these products to aid in tobacco cessation smoking. Due to the complexities surrounding its beneficial use against tobacco use and potential health effects, uncontrolled and understandard quality products render vaping through these E-cigarettes a major public health issue.^[8]

Therefore, the purpose of this review is to understand many important aspects regarding vaping and answer some questions such as what is vaping, why it is more enticing to adolescents and young adults, what makes it more harmful than regular smoked tobacco products, health consequences by their use, and what measures are currently being taken against this activity.

Methodology

Search strategy

A systematic literature search was conducted in online database PubMed using search string “((((Lung injury*[Title/Abstract]) AND Vaping[Title/Abstract]) OR electronic nicotine delivery device[Title/Abstract]) OR electronic cigarette*[Title/Abstract]) AND e-cigarettes liquid) AND electronic cigars and search filter used were “published in the last 5 years” and “Human Studies.” Similar search terms were used to search EMBASE, Web of Science, Google Scholar, and the CENTRAL database of the Cochrane Library with the help of Boolean terms [Flowchart 1].

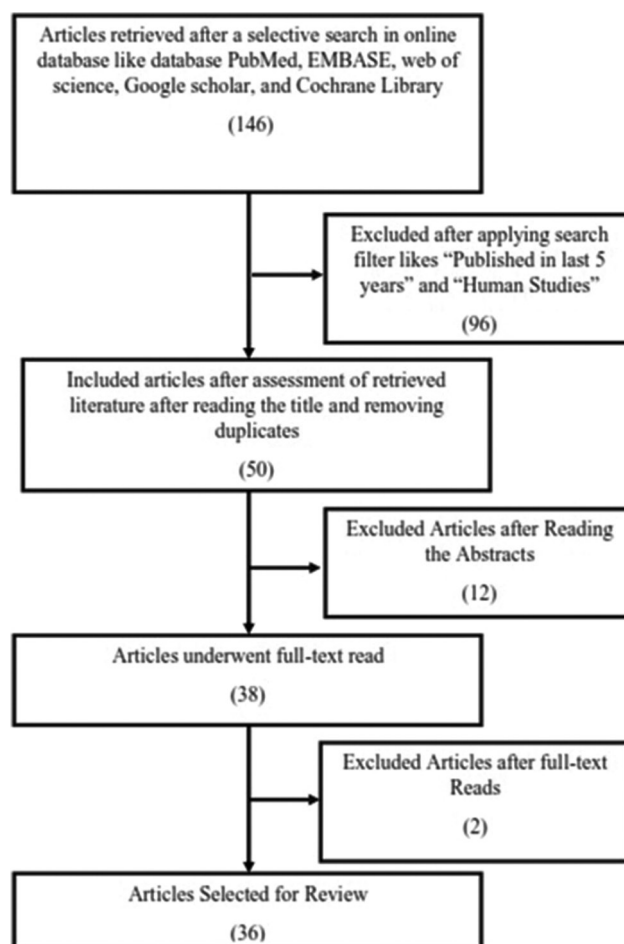
Selection criteria

Data extraction was performed by authors (HS and SV) from the full-text reads of the selected for articles inclusion. All written papers related to vaping by electronic devices, E-cigarettes or electronic nicotine delivery systems (ENDS), and lung injury have been included due to limited literature on the topic of interest. Moreover, those papers who failed to meet the inclusion criteria were excluded.

What is vaping?

According to the Merriam-Webster Dictionary, vape or vaping is to inhale vapor through the mouth from an electronic device that is normally powered by batteries (such as an electronic cigarette) that heats up and vaporizes a liquid or solid.^[9]

According to the Bill passed by the Ministry of Health and Family Welfare, “The Prohibition of Electronic Cigarettes (Production, Manufacture, Import, Export, Transport, Purchase, Distribution, Storage and Advertising) Act, 2019,” electronic cigarettes (E-cigarettes) are classified as electronic devices that heat a substance that may contain nicotine and other chemicals to produce inhalation vapor.



Flowchart 1: Flowchart for selection of articles

Such E-cigarettes may also contain various types, including all forms of ENDS, heat-not-burn products, E-hookahs, and similar devices.^[10]

What makes vaping more appealing to youth and young adults?

Most E-cigarettes at the end are fitted with a light-emitting diode to mimic the appearance of a normal burning cigarette. Traditional devices through heating elements produce a vapor of nicotine that is suspended in a propylene glycol and glycerin mixture. Using different cigarette-looking devices and tempting E-cigarette blends, vaping looks fun and fashionable, and when the vapor is inhaled, it gives the user a sensation in their mouth and throat identical to smoking regular filtered cigarettes. However, the related physical activity of vaping, such as raising the tool to the mouth, inhaling and exhaling smoke, is similar to smoking and may lead to new addicts.^[11]

Along with these, nowadays, most of the brands provide the option to smoke a variety of materials promoting customizable devices to meet user demands. Such customizable vaping devices can be replenished with liquids of a variety of flavors and nicotine brands from

local markets and online stores and can be conveniently replenished by watching videos on most online pages. This helps them to vape a variety of flavor and nicotine concentration via altering the vaporizing power of the device by variable voltage, current, and temperature. Alternatively, consumers can purchase readymade or base formulations that can be blended with flavors to match individual preferences for taste, density of vapor, visibility and amount, and sensation and concentration of nicotine.^[12]

Currently, kid-friendly flavored E-cigarettes and cigars are aggressively marketed by manufacturers in enticing flavors such as gummy bear, cherry crush, and banana smash, which may lure children and young adults to this vaping habit. Such flavors are advertised primarily in the name of products generally recognized as safe (GRAS) and mean that the product or material added to the E-cigarette liquid for flavoring is considered safe by experts and is therefore excluded from the normal provisions of the Federal Food, Drugs and Cosmetic Act.^[13]

A research conducted by Zhu *et al.* revealed the ugly side of the E-cigarette industry and reported that, by January 2014, there were approximately 7764 different flavors of 466 E-liquid brands each with their own website. Moreover, there had been net surge of 10.5 brands and 242 new flavors per month in 17 months between their searches.^[14,15]

According to a report published by Times of India on May 26, 2019, about 6.25 lakh children have been reported to smoke. A recent surprise inspection at a popular school in East Delhi has resulted in the discovery of a large number of vaping devices from the students. The trend of vaporizing equipment used by school students is steadily increasing as students are tempted by a variety of vaporizing flavors such as lemon, strawberry, fruit medley, banana, and cucumber. Even after a large number of students are involved in the act, it is difficult to catch errant students as there is limited or no odor emitted from such devices.^[16]

Does particle size of the inhaled aerosol matter?

Although vapor inhaled by E-cigarette is believed to contain fewer particles of larger size, it still poses a threat to the respiratory tract by exposing individuals to ultrafine particles. Some researchers have shown that vaping by E-cigarettes creates ultrafine particles with a diameter of <100 nm; the concentration of which in the inhaled aerosol depends on puffing times and nicotine content.^[17]

The ultrafine particles generated by cartomizer fluid comprise particles of more than 1 µm consisting of gold, silver, iron, nickel, aluminum, silicate, and nanoparticles and <100 nm of tin, chromium, and nickel.^[7]

Such highly concentrated ultrafine particles can pose a high toxicological risk to the respiratory tract and lungs as their

deposition is significantly higher than particles of regular smoked cigarettes.^[18]

What makes vaping more dangerous?

Vaping cannabis-related products (VCRPs) such as tetrahydrocannabinol (THC) in the form of cannabinoid oils are considered safe and much more pleasurable compared to cannabis-related products as inhaling smoke from a dried cannabis plant is thought to pose a higher risk of adverse effects. The VCRPs show perceived advantages over smoking as it provides better taste, more extreme effect, and flexibility of being able to use at any place.^[19]

In addition, THC vapers tend to inhale deeply and hold their breath together with the smoke for long periods of time to get maximum pleasure, executing a Valsalva maneuver (forced attempted exhalation against a closed airway) at optimum breath-hold.^[20]

A report published in the Morbidity and Mortality Weekly Report (MMWR) reports that many of these product companies use potentially hazardous additives such as Vitamin E acetate, medium-chain triglyceride oil, and other lipids to manufacture liquids for these vaping products. In particular, Vitamin E acetate has indeed been added to E-cigarette liquid or vaping products to serve as a thickener in THC products. Vitamin E acetate inhalation can impair the function of the lung.^[21]

Another report published in the MMWR describes features of uglier side of E-cigarette product use by patients in Illinois and Wisconsin. The reports state that out of all the comprehensive interviews conducted on the patients, 96% of individuals used THC-containing products that were packed, prefilled cartridges. Of these consumers, 89% purchased prefilled cartridges from informal sources (e.g., friends, family members, and unauthorized or off-street dealers) whose chain for production and distribution is unclear. In view of the high number of patients suffering from lung injury involved in vaping these THC-related products, the Centers for Disease Control and Prevention (CDC) had advised that all persons should consider refraining from using E-cigarette or vaping products, particularly those containing THC, until the investigation is in progress.^[22]

However, most of the individuals remain unaware of the fact that science of vaping is still at its infancy with very less known about the benefits and adverse effects. In addition, many of the nicotine-based vaping products contain specially formulated nicotine and higher amounts of benzoic acid, thus increasing nicotine potency, rendering the vapor less harmful, and creating a “spiking” effect that makes it easier for consumers to inhale more nicotine for longer periods. Regular use of these nicotine-based vaping products with high concentration of nicotine may lead to nicotine dependence and may lead to combined use of vaping devices along with combustible forms of tobacco.^[23,24]

Many of current vaping products come with options of certain flavoring agent. Tobacco companies perceive their products to be safe, claiming that the flavoring agents are not harmful as they are all “food grade” and “GRAS.” However, the option to purchase base formulations that can be blended with flavors to adjust to subjective desires and commercially available readymade cartridges with potentially toxic levels of flavoring agents found by Farsalinos *et al.* 2015 and existing evidence of irritation and inflammation of the respiratory and cardiovascular systems to such high levels of flavoring agents makes it a public health concern.^[25]

It is evident from the literature that individual exposure depends on a number of variables, such as product voltage, temperature, taste of different e-liquids, nicotine content/density of vapours emitted, air flow rate, vapour pressure drop and individual smoking behavior, making it difficult to scientifically assess the threshold for such exposures and toxicological outcomes in humans. Many of the companies now market customizable devices that can be used to vape varieties of products through these devices. These customizable products allow the user to change the resistance and voltage of atomizer through replaceable parts and adjustable dials. Hence, such self-adjustable vaping devices pose a threat by altering the composition of aerosols generated by inhaling the same E-liquid through different devices.^[26]

It is also of concern that these vaping devices with adjustable heating temperature can be used to vape recreational drugs and new psychoactive substances, information for which is easily available on social media, and several internet drug forums. Hence, it makes it much appealing to the youth for vaping cannabis and creates the negative image of these vaping devices that E-cigarettes are not just for nicotine use.^[27]

Health consequences of vaping

The habit of vaping and smoking among adolescents and young adults has grown steadily. Vaping nicotine, THC, or simply vaping with flavoring liquids for fun are very effective ways to inhale dangerous quantities of fine and ultrafine particulate matter. Long-term use may have a detrimental effect on brain health due to cerebral oxidative stress, which is very similar to smoking-related oxidative stress.^[28]

Even in small quantities, inhalation of nicotine results in local and systemic release of catecholamine, which leads to increased heart rate, blood pressure, and heart contraction. In addition, there is a marked decrease in cutaneous and coronary blood flow along with increased skeletal muscle blood flow leading to reduced myocardial oxygen delivery, contributing to myocardial ischemia and cardiovascular disease.^[29]

Long-term nicotine inhalation promotes the release of basic fibroblast growth factor while inhibiting indigenous

production of transforming growth factor- β 1 resulting in increased endothelial cell proliferation due to increased mitogenic activity that ultimately leads to atherosclerotic plaque formation that is further aggravated by neovascularization stimulated by nicotine.^[29,30]

In addition, many of these vaping products are loaded with a solution containing known carcinogenic effects when inhaled such as carbonyl compounds (formaldehyde, acetaldehyde, acrolein, and o-methylbenzaldehyde), volatile organic compounds (toluene and p, m-xylene), tobacco-specific nitrosamines, and metals (cadmium, nickel, and lead).^[6,8,31,32]

Although it is known that various potential carcinogens may already be present in unregulated e-liquids, they are often equipped with uncontrolled and user-adjustable heating elements that may further contribute to the development of other carcinogens, such as formaldehyde-containing hemiacetals, due to high-temperature heating solutions. It was shown in one of the *in vitro* studies that vapor produced by these vapor devices causes DNA strand breaks and cell death independent of nicotine content.^[33]

The MMWR released on November 8, 2019, reported that, when testing THC-containing product samples collected by the Food and Drug Administration (FDA) and state public health labs were analyzed, a number of additives were identified. They reported finding potentially hazardous Vitamin E acetate from bronchoscopy and bronchoalveolar lavage (BAL) of all patients suffering from E-cigarette, or vaping, product use-associated lung injury (EVALI), which may be a potential additive related to the injury. Researchers also suggested that although more than one compound or component could be a source of lung injury, there is still insufficient evidence to rule out the association of other toxicants with EVALI.^[21]

Many of these EVALI patients reported having respiratory symptoms such as cough, chest pain, and shortness of breath, while some reported gastrointestinal symptoms such as abdominal pain, nausea, vomiting, and diarrhea with constitutional symptoms such as fever chills and weight loss. Therefore, as suggested by a report published by CDC on November 19, 2019, since EVALI patients may have symptoms similar to those associated with influenza or other respiratory infections, it may be difficult to distinguish EVALI from influenza or community-acquired pneumonia upon initial assessment, and EVALI may co-occur with respiratory infections, thus making it difficult to identify and treat.^[34]

Diacetyl (2,3-butanedione), a very popular flavoring agent providing a buttery or creamy flavor, has been shown to trigger an acute onset of bronchiolitis obliterans, an irreversible pulmonary obstructive disease often referred to as "popcorn lung" when used daily.^[35,36]

Eugenol (phenylpropene) and cinnamaldehyde (α , β -unsaturated aldehyde) are the main components of clove oil, cinnamon-flavored additives applied to the E-cigarette liquid to obtain such blends of flavors, both of which are classified as asthma sensitizers. Likewise, benzaldehyde is a recognized irritant to the mucous membranes of the respiratory passages that are widely used to make cherry or fruit flavored and liquids.^[36]

Some of the other flavoring agents that are known as Airway Irritants and Chemical Sensitizers are diacetyl, acetoin, 2,3-pentanedione (buttery flavors), camphor and cyclohexanone (minty flavors), benzaldehyde (cherry or almond flavors), cinnamaldehyde (cinnamon flavors), cresol (leathery or medicinal flavors), butyraldehyde (chocolate flavors), and isoamyl acetate that provides (banana flavor).

In a correspondence published by Butt *et al.* in 2019, histopathological findings showed patterns of acute lung injury, including acute fibrinous pneumonitis, diffuse alveolar damage, or pneumonia, typically bronchiolocentric, and accompanied by bronchiolitis. In the two cases where BAL fluid was available for analysis, it was seen that it contained abundant foamy macrophages. Two patients with diffuse alveolar damage suffered death despite the effective treatment.^[37]

Steps taken to curb the practice in globally

On May 21, 2003, an appreciative step was taken by the WHO by formulating a treaty, i.e., Framework Convention on Tobacco Control (FCTC) and had urged all its signatories to adopt treaty and consider banning or restricting E-cigarettes to reduce the potential health risks associated with them which came into force on February 27, 2005.^[38]

Thereafter, several researchers advocated that there is insufficient scientific evidence to prove the safe use of ENDS and vaporizing devices and their beneficial contribution to the cessation of tobacco smoking habit, so it is pointless to mark it as safe and legal. Currently, more than 30 countries, including Argentina, Brazil, Brunei, Cambodia, Egypt, Indonesia, Jordan, Lebanon, the Philippines, Malaysia, Mexico, Oman, Qatar, Singapore, Taiwan, Thailand, Turkey, the United Arab Emirates, Uruguay, and Vietnam, have imposed a ban on the manufacturing, import or sales of E-cigarettes or vaping devices in some or the other ways, while the countries which had placed restrictions on manufacturing, import or sales of E-cigarettes or vaping devices are Australia, Canada, Norway, Japan, United States, and Hong Kong.^[10,39]

The U.S. FDA via FDA voice on September 10, 2019, states that ENDS such as E-cigarettes, cigars, pipe tobacco, and hookah tobacco already on the market as of August 8, 2016, must submit a premarket authorization application to FDA by May 12, 2020, at the latest. However, on the

other hand, any E-cigarettes or other ENDS products that have not been marketed as of August 8, 2016, need to receive marketing authorization from the FDA before the product can enter the market or are subject to enforcement. FDA is actively monitoring ENDS and vaping products that use any flavored cartridge or refills, products whose manufacturer failed or failing to take adequate measures to prevent minors' access, and products that are targeted to minors or that may be unlawfully on the market and has released letters to about 90 companies seeking information on more than 110 brands to assess whether those items are being inappropriately sold. Moreover, as of now, the FDA had issued warning letters to six companies notifying them of the need to remove from the market a combined 71 products.^[40,41]

As part of WHO, FCTC India was not behind, and Punjab and Haryana were India's first states to ban E-cigarettes or ENDS under the Poisons Act, 1919, which not only promoted the significant decrease of practice across the country, but also helped raise awareness of ill effects.^[42] Indians have taken a very appreciative measure by formulating an ordinance on the use of these vaping tools, known as the "Prohibition of Electronic Cigarettes (Production, Manufacture, Import, Export, Transport, Purchase, Distribution, Storage and Advertising) Regulation, 2019." This Act prohibits the manufacture, trade, and advertising of e-cigarettes in India, and any person found to be in violation of this Act shall be punished by imprisonment of up to one year or a fine of up to one lakh rupee or both. This also states that no person is permitted to use any place to store any stock of E-cigarettes or vaping products, and if someone is found to be in violation, he will be punished with up to 6 months' imprisonment or a fine of up to Rs. 50,000 or both.^[42]

Conclusion

From the current systematic review, we would like to emphasize that no long-term toxicological and health studies have been carried out in humans using these vaping products and their constituents to date. Without these studies, it is impossible to say with confidence that vaping through E-cigarettes is safer than fuel cigarettes. Many of the studies and reports indicate the prevalent use of prefilled cartridges sold in informal and unregulated markets whose chain of production and distribution is unreliable. Many of the known brands use additives such as flavoring and thickening agents that, when used even for the short term, can cause toxicity to human lung tissues. This toxicity depends not only on the extent of the habit, but also on the variable susceptibility to lung damage, dual-use with cigarettes, variability in the product design of different brands, and the liquid content used in them. Although cessation should be strongly encouraged in smokers for a better quality of life, it is uncertain whether it is a universally safer option to replace cigarettes with these vaping devices. Although an appreciative step was taken by

the Indian government by banning the use of such vaping devices, as an author, we recommend that further research should be carried out before recommending it as a possible aid to combat the use of tobacco.

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Conflicts of interest

There are no conflicts of interest.

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