An Epidemic Supplanted by a Pandemic: Vaping-Related Illness and COVID-19

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Abstract: Before the coronavirus disease 2019 (COVID-19) pandemic, vaping-related illness was the prevailing public health concern. The incidence of vaping-related illnesses—mainly e-cigarette, or vaping, product use–associated lung injury (EVALI)—went from a peak in September 2019 to a low in February 2020, and the Centers for Disease Control and Prevention decided to discontinue the collection of EVALI case reports. Despite the decrease in EVALI with the arrival of COVID-19, EVALI should still be considered a differential diagnosis for people with COVID-19 for reasons outlined in this review. This narrative review describes vaping devices, summarizes the adverse health effects of vaping on the lungs and other systems, considers the potential interplay between vaping and COVID-19, and highlights gaps in knowledge about vaping that warrant further research.

Key Words: COVID-19, e-cigarettes, EVALI, vaping

Although easily forgotten in the midst of the coronavirus disease 2019 (COVID-19) pandemic, a major outbreak of vaping-related illness dominated public health concerns before the arrival of severe acute respiratory syndrome-coronavirus-2. This narrative review describes vaping devices, summarizes the adverse health effects of vaping on the lungs and other systems, considers the potential interplay between vaping and COVID-19, and highlights gaps in knowledge about vaping that warrant further research.

Historical Background

Electronic cigarettes, or e-cigarettes, also known as vaping devices, are electronic nicotine delivery systems designed to simulate smoking by delivering an aerosolized mixture. The mixture usually contains nicotine, flavor, and a delivery system commonly made of propylene glycol or glycerin.[1–3] The first smokeless nontobacco cigarette was invented by Herbert A. Gilbert in 1965.[4] The objective was to provide a safe and harmless means of smoking by replacing burning tobacco and paper with heated, moist, and flavored air. In addition, Gilbert wanted to create a method by which warm medications could be introduced into the lungs in case of a respiratory ailment through inhalation.

The first e-cigarette entered the Chinese market in 2003 and the US market in 2007.[5] Since the introduction of e-cigarettes to the US market, marketing has increased and the design and manufacturing process has continued to evolve. E-cigarettes were initially marketed as a healthier alternative to conventional tobacco cigarettes, especially as the list of health hazards caused by conventional tobacco cigarettes continued to grow.[6] Proponents of e-cigarettes claim that these products give users a satisfying smoking experience, without exposure to the toxic components of conventional cigarette smoke. They argue that switching to e-cigarettes will be of public health benefit.[7] By 2014, e-cigarettes had expanded to 466 brands and 7764 different flavors.[8] These products are widely available online and in retail outlets, especially in neighborhoods with a higher household income[9] and in states with weak laws for clean indoor air and with low taxes on cigarettes.[7]

Tobacco control efforts cut the youth cigarette smoking rate in half from 1997 to 2007 and estimated to have saved more than 8 million lives during the past 50 years.[10,11] E-cigarettes, varying in power and potency, typically contain a nicotine-based liquid that is vaporized. The introduction of e-cigarettes is known to have increased the use of nicotine-containing products among youths.[12] E-cigarettes become a gateway to smoking by exposing young people.[12] Since 2014, e-cigarettes have been the most commonly used tobacco product among youths.[12] In 2019, approximately 1 in 4 youths (23.0%) had used a tobacco product during

Key Points

- Electronic cigarettes (e-cigarettes) have gained popularity, especially in youths.
- E-cigarettes have continued to evolve over the years, with increases in customization for the consumer.
- E-cigarettes have been linked to lung injury known as e-cigarette or vaping product use–associated lung injury.
- With the rise of coronavirus disease 2019, there have been far fewer cases of e-cigarette or vaping product use–associated lung injury, but it should still remain a differential diagnosis.

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the past 30 days. This is approximately 3 in 10 high school students (31.2%) and approximately 1 in 8 middle school students (12.5%).[13] In 2020, the current use of any tobacco product was reported by 16.2% (4.47 million) of all students, including 23.6% (3.65 million) of high school students and 6.7% (800,000) of middle school students. E-cigarettes were the most used tobacco product among high school (19.6%; 3.02 million) and middle school (4.7%; 550,000) students.[3] Awareness and use of e-cigarettes also increased considerably among US adults during 2010 through 2013. In 2013, more than one-third of current cigarette smokers reported that they had used e-cigarettes.[14]

How E-Cigarettes Work

E-cigarettes are battery-powered devices with four components: a solution cartridge, a vaporizing chamber, a heating element, and a battery.[1] The solution cartridge contains refillable or exchangeable liquid (vape liquid or e-cigarette liquid) that usually includes nicotine, flavoring, and a delivery system (propyleneglycol or glycerin or even both). The composition of the liquid and the concentration of the substances in the liquid are variable and at times inconsistent with the label.[15]

The heating element provides heat to the liquid chamber for aerosolization of the liquid containing nicotine and other substances. Most e-cigarette models give the user the option to select the amount of aerosol produced and the nicotine concentration. The aerosol is usually held in a chamber with the heating element until use.[1]

The battery supplies power to the heating element, which aerosolizes the solution in the liquid chamber. The size and shape of the battery contributes to the size and shape of the e-cigarette.[1] The power is turned on manually or automatically. E-cigarettes with an automatic button function like regular cigarettes in that inhalation activates the device, whereas e-cigarettes with a manual battery have a button that must be pressed to activate the device to produce heat.[16] Some of the batteries can overheat and explode if inappropriately charged. Explosions also have been reported from mistaken attempts to light up these cigarettes with a flame lighter.[1] E-cigarettes have continued to evolve from first-generation devices in size, shape, and ability to customize. The second-, third-, and fourth-generation devices allow for different types of customization.

First-generation e-cigarettes look like conventional tobacco cigarettes. They are battery operated and have an atomizer and a cartridge. In the most recent first-generation e-cigarettes, the atomizer (responsible for heating up the liquid) and the cartridge have been replaced by the cartomizer, which is an atomizer and a cartridge combined. The cartomizer then connects to the battery. Some of them are one-time-use batteries, while others have a rechargeable battery. These devices are available with different flavors and nicotine concentrations.[7]

Second-generation e-cigarettes are usually larger, with higher capacity batteries and larger separate refillable cartridges or tanks. Cartridges in second-generation e-cigarettes are refillable with various types of e-cigarette or vape liquid. Some second-generation e-cigarettes have a manual switch that allows the user to regulate the frequency and length of puffs.

Third-generation e-cigarettes are similar to second-generation e-cigarettes, but they allow for more customization and are therefore also known as personalized vaporizers or aerosols.[7] They come with a large range of battery and atomizer options. Some devices allow the user to adjust the resistance of the atomizer to produce higher heating temperatures. Users also can pair different atomizers with high-capacity batteries to increase vapor production and battery life.[7]

Fourth-generation e-cigarettes are rechargeable devices with replaceable cartridges that contain nicotine and flavorings. They are also known as "pod-mod devices" and are increasingly popular among adolescents[17]; JUUL is a popular brand (it looks like a thumb drive). These devices contain nicotine in a form that is less irritating to the throat and thus tend to deliver higher concentrations of nicotine.

Health Effects of E-Cigarettes

E-cigarettes have been associated with adverse effects on multiple organ systems as summarized in the Table. Lung injuries are the most widely recognized adverse effects of e-cigarettes, capturing the attention of the Centers for Disease Control and Prevention (CDC) and public health officials before the arrival

Table. Effects of e-cigarettes on various organs and systems

System	Clinical findings
Pulmonary	Irritation of the upper and lower airways Bronchitis/pneumonia (acute eosinophilic pneumonia, organizing pneumonia, lipoid pneumonia)[18,19] Acute respiratory distress syndrome and hypersensitivity pneumonitis Increased risk of asthma in children[2] Cough Emphysema Nasal mucosa atrophy and ulcerations
Cardiovascular	High blood pressure Increase heart rate Arrhythmias[20] Acute myocardial infarction[21] Oxidative stress[21]
CNS	Mood changes Behavior changes[22,23] Tremor and muscle spasms[22] Headaches[2] CNS damage[24,25]
Immune system	Induced inflammatory effects[26] Reduce immune response[27]
GI system	Nausea and vomiting Irritation[28] Gastric distress[2,29]
Reproductive system	Reduce fertility and reproduction[2]
Others	Nephrotoxicity Hepatotoxicity Ocular irritation[28] Dermal irritation[28]

CNS, central nervous system; e-cigarettes, electronic cigarettes; GI, gastrointestinal.

of COVID-19 in the United States in 2020.[30,31] The effects of e-cigarettes on the lungs and other organs are caused by the some of the common chemicals produced by e-cigarettes listed below[2]:

- Aldehydes: acetone, acetaldehyde, formaldehyde
- Volatile organic compounds: glycerin, propyleneglycol, toluene
- Nitrosamines
- Nicotine
- Metals: chromium, cadmium, lead, and nickel

E-Cigarettes or Vaping Product Use–Associated Lung Injury

Although e-cigarettes were touted to be much safer than conventional cigarettes, there is substantial evidence of e-cigarette-associated lung injury. The respiratory system has direct exposure to vapor and smoke from e-cigarettes, causing direct irritation to both upper and lower airways.[23,32,33] As e-cigarette and vaping product use has increased, there has been a growing number of cases of a new disease process known as e-cigarette or vaping product use–associated lung injury (EVALI). In 2019, the Wisconsin Department of Health Services and the Illinois Department of Public Health investigated a series of patients with lung injury related to e-cigarette or vaping use. From this investigation, 98 patients from Wisconsin and Illinois were identified who were suspected to have EVALI. They found that respiratory and gastrointestinal symptoms were common, occurring in 97% and 77% of patients, respectively. Most of the patients had shortness of breath, cough, chest pain, nausea, vomiting, and diarrhea. A majority of patients had constitutional symptoms, including subjective fevers and chills. EVALI is a diagnosis of exclusion.[34] The patient must have used vaping within the past 90 days, other etiologies must be eliminated, and chest imaging findings must be abnormal.[35] As part of the evaluation for EVALI, patients obtained chest X-ray and/or chest computed tomography (CT). They found that more than 80% of patients had an abnormal chest x-ray and 100% of patients had abnormal findings on chest CT.[36] On CT scans, EVALI manifests as acute lung injury similar to hypersensitivity pneumonitis with multifocal ground glass opacities, often with organizing consolidation, diffuse alveolar damage, and a small centrilobular nodular pattern.[37,38] Other less common forms of lung injury, including acute eosinophilic pneumonia and diffuse alveolar hemorrhage, also have been reported.[35]

As of February 2020, there have been more than 2800 cases of EVALI reported to the CDC, with approximately 68 deaths attributed to this illness.[39] Cases of acute eosinophilic pneumonia, organizing pneumonia, acute respiratory distress syndrome, and hypersensitivity pneumonitis have been described as well.[40] No single substance has been found responsible for EVALI or EVALI-associated deaths, but the main ingredients that seem to cause lung injury are tetrahydrocannabinol (THC), nicotine, and vitamin E acetate (which is an additive in THC products).[30,31,40,41] The CDC found that 82% of EVALI patients reported using THC-containing products. A majority of these patients obtained their products from informal sources, such as friends, family, in-person dealers, or online dealers. In addition, the CDC found that among those patients who reported using nicotine-containing products (57%), a majority obtained their products through commercial sources, such as medical and recreational dispensaries, vape shops, or smoke shops. THC-containing products obtained from informal sources contain traces of vitamin E acetate, which is believed to contribute to EVALI.[30] One study looking at the bronchoalveolar lavage fluid showed vitamin E acetate was present in 945 of EVALI patients but none in the healthy controls.[13] This suggests that vitamin E acetate may be a primary cause of EVALI. Nevertheless, patients who report using nicotine-only products also have been diagnosed as having EVALI, raising concerns that components other than vitamin E acetate may stimulate lung injury.[30] More studies are needed to pinpoint the cause.

The mechanism of lung injury from e-cigarettes is not completely understood. As e-cigarette liquid is heated, it aerosolizes heavy metals such as tin, iron, nickel, lead, and chromium and produces tobacco-specific *N*-nitrosamines, polycyclic aromatic hydrocarbons, and volatile organic compounds.[42,43] Propyleneglycol and glycerol are the major ingredients used as the delivery system for e-cigarettes. Exposure to propyleneglycol mist may occur from smoke generators used in nightclubs, theaters, and aviation emergency training. Wieslander et al studied the health effects from occupational exposure to propyleneglycol and found that exposure to propyleneglycol for as little as 1 minute results in upper airway irritation in nonasthmatic subjects.[43] A few participants in this study developed a cough and slight reduction in forced expiratory volume in 1 second and forced vital capacity.[43] A minute amount of heavy metals has been found in some e-cigarette vapors.[44] It is unclear how these small amounts of heavy metals affect the lung mechanics over a long period of time.[7]

Another area of lung health interest with e-cigarettes is the potential effects on the immune system of the lung. Reidel et al studied sputum samples in e-cigarette users and found that e-cigarette users had increased oxidative stress–related proteins, increased levels of innate defense proteins, increased immune response proteins, and a change in the composition of airway mucus.[45] A study from Greece found that the use of e-cigarettes for even 5 minutes caused an increase in airflow resistance, a decrease in exhaled nitric oxide, and an increase in oxidative stress.[46] Even a brief exposure to e-cigarettes caused altered lung function on a cellular level. There were changes in gene expression that could increase inflammation, decrease host defense mechanisms, and increase protumorigenic signals.[46]

Vaping and COVID-19

Hospitalizations for EVALI reached a peak in late 2019 and rapidly declined to extremely low numbers of reported cases by January 2020, just before the initial identification of COVID-19 cases in the United States.[47] Although vaping-related illness may have nearly disappeared as a consequence of increased public awareness resulting in risk reduction by users and by removal of vitamin

E acetate from vaping products, a case report of a patient in April 2020 reminds clinicians that EVALI should remain in the differential diagnosis for young patients admitted with severe lung injury.[48] Presenting symptoms of EVALI (dyspnea, cough, fever, nausea, vomiting, and diarrhea) overlap with those of COVID-19,[36,49,50] and during population surges of the pandemic there is a tendency to narrow diagnostic considerations. As noted previously, EVALI is considered a diagnosis of exclusion, particularly exclusion of infectious etiologies, but critical to making the diagnosis is asking patients about vaping exposures.

Similar to clinical presentation, imaging findings for EVALI and COVID-19 demonstrate significant overlap.[51] Chest radiography in EVALI typically shows bilateral multifocal ground glass opacities or symmetric consolidation with lower lung zone predominance. Similarly, in COVID-19 the chest X-ray may initially appear normal, although typical findings include patchy bilateral ground glass opacities and/or consolidation that is peripheral and lower lung predominant. Chest CT in EVALI typically demonstrates bilateral symmetric ground glass opacities with or without consolidation predominantly in the lower lobes with subpleural sparing. Chest CT in COVID-19 shows similar findings, although peripheral and subpleural distribution is common. Subpleural sparing should prompt consideration of EVALI instead of COVID-19.[52]

Other potentially useful clues to EVALI include leukocytosis versus normal or low white blood cell count with associated lymphopenia seen with COVID-19.[53] Some authors have suggested that rapid response to corticosteroids also may favor EVALI in young patients with extensive lung findings.[53]

An online survey of 4351 adolescents and young adults (ages 13–24) reported an increased risk of self-reported COVID-19 illness among users of e-cigarettes.[54] This study received substantial attention in the media but also was criticized for methodologic flaws. Although convincing evidence is lacking, it seems plausible that e-cigarette usage would increase the risk of severe COVID-19 lung injury and may increase susceptibility to the infection.

Conclusions

Before the overwhelming impact of the COVID-19 pandemic, EVALI presented as an emerging epidemic that has now subsided, although there is a risk of overlooking this illness in our evaluation of patients with severe respiratory illness. The overlap of symptoms, signs, and imaging findings seen with these two conditions poses diagnostic challenges and emphasizes the importance of asking patients about vaping. The emergence of vaping-related illness also serves as a reminder of the need to be vigilant for adverse effects of seemingly less harmful habits and the risks these may pose to our patients.

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