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Vaping in adolescents: epidemiology and respiratory harm

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Abstract

Purpose of review—This review highlights epidemiologic changes in e-cigarette use in adolescents, discusses recent advances in aerosolized nicotine delivery, and provides and updated profile of research related to the lung-specific harm of e-cigarettes.

Recent findings—In the past decade, nicotine-containing e-cigarettes have emerged as the most popular tobacco and nicotine delivery modality among adolescents in the United States.[1] The surge in popularity of these devices has coincided with an outbreak of vaping-related lung injury, bringing e-cigarette use to national attention, and creating a great deal of confusion regarding their potential for respiratory harm. Newer pod-based devices and formulations of e-liquids have resulted in products appeal to youth and deliver nicotine with increasing efficiency. E-liquid aerosols are associated with direct harm to respiratory epithelium and have been shown to alter pulmonary function, inflammation, mucociliary clearance, and lung histology.

Summary—Although the long-term harms of regular e-cigarette use are unknown, numerous studies including early longitudinal data suggest e-cigarette use is associated with incidence of respiratory disease, independent of concurrent traditional cigarette use. Improved understanding and recognition of harm will contribute to the basis of further studies examining the role of e-cigarettes on chronic respiratory disease and will inform future prevention education.

Keywords

E-cigarettes; e-liquid; EVALI; smoking cessation; vaping

INTRODUCTION: E-CIGARETTE USE IN ADOLESCENTS IN THE UNITED STATES

Since their introduction to the United States tobacco market in 2007, e-cigarettes have gained widespread popularity among adolescents. Although they were originally developed

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There are no conflicts of interest.

as a tobacco cessation tool, vaping has become pervasive among middle and high school students, with epidemic rates of e-cigarette use observed starting in 2017. Although combustible cigarette use among youth began a precipitous decline since the late 1990s, e-cigarette use among high school students surpassed combustible tobacco use for the first time in 2014, a trend that continued to widen into 2020 [1].

Monitoring the future surveys of over 43 000 students throughout the US report yearly rises in nicotine vaping among middle and high school students since 2016, the largest increase of which occurred between 2017 and 2018. During this time period, past-12-month use of electronic cigarettes nearly doubled among 12th graders, from 11% to 21%, representing the greatest increase in use of any substance recorded in all Monitoring the Future data [2■■]. By 2019, 35% of 12th graders reported past-12-month use of e-cigarettes, with approximately 1 in 4 reporting past-30-day use, and 1 in 9 reporting daily use [3■■].

Following the 2018 Monitoring the Future report, the US Surgeon General Dr Jerome Adams and the then FDA Commissioner Dr Scott Gotlieb declared e-cigarette use among adolescents an 'epidemic.' Despite national attention, vaping among adolescents continued to rise in the United States. JUUL, a pod-based e-cigarette that uses its proprietary cartridge-based nicotine controlled approximately 70% of the US e-cigarette market at that time. The rapid rise in prevalence of Juul pods, which contain the amount of nicotine found in 1.5–2 packs of cigarettes [4], was attributed to the rise in adolescent e-cigarette usage and resultant numbers of youth addicted to nicotine.

Over 60% of middle and high school students participating in the 2019 National Youth Tobacco Survey named JUUL as their primary e-cigarette brand, with the next highest brand SMOK named by 7.8% of participants. Flavored e-cigarettes were preferred by 59% and 72% of middle and high school exclusive e-cigarette users, respectively, with the most common categories being fruit (66.1%), 'mint or menthol' (57.3%), and 'candy, desserts, or other treats' (34.9%). Mint or menthol flavors were shown to have the greatest increase in overall use, tripling from 2016 to 2019, and nearing popularity of fruit-based flavors by 2019 [1].

SMOKING CESSATION, INITIATION, AND RISK PERCEPTION

The focus of e-cigarette use has been divided into two subtypes of users: active smokers seeking to quit traditional cigarettes, and recreational users. In the former, e-cigarettes have been acknowledged by many as an effective tool for smoking cessation. When compared to other forms of nicotine-replacement therapy (NRT), e-cigarettes have been found to be modestly effective at best in helping smokers achieve abstinence from cigarettes.

A 2013 study published in *The Lancet* showed similar rates of abstinence in adult smokers using e-cigarettes compared to nicotine patches, with abstinence defined as use of fewer than 6 cigarettes smoked in the 6-month follow-up period. The overall rate of abstinence reached a rate of 7.3% in the e-cigarette group [5]. However the question of whether e-cigarettes could provide long-term abstinence remained unanswered. A 2019 randomized controlled trial published in *The New England Journal of Medicine* attempted to address this question by comparing one-year abstinence rates in smokers assigned to either nicotine-containing e-cigarettes or other forms of NRT such as patches or gum, both in conjunction with cognitive behavioral support. This study reported 18% abstinence in the e-cigarette group compared to 9.9% in the NRT group, suggesting that e-cigarettes may be more effective than other forms of NRT when combined with individualized therapy [6■]. However, 80% of users in the e-cigarette group who reported abstinence continued to vape at 52 weeks compared to 9% of successful NRT-group participants. As such, people were more likely to switch from one tobacco product (cigarettes) to another (e-cigarettes), rather than quit nicotine and tobacco altogether. A recent study by Gomajee *et al.* [7] has suggested that continued use of e-cigarettes by former smokers is associated with reinitiation of cigarette smoking.

With regard to recreational users, a specific focus on youth vaping culture has emphasized the potential for nicotine addiction in youth who have never smoked traditional cigarettes [8]. Monitoring the Future data from 2019 showed a two-fold likelihood of ever-use of e-cigarettes compared to combustibles and five-fold prevalence of past-month use among 12th graders [9■■]. The relationship between vaping and cigarette smoking initiation has been a subject of scrutiny in recent years, with numerous studies reporting a correlation between e-cigarette exposure and uptake of cigarette smoking among adolescents and young adults [10–12]. A 2018 report from the National Academies of Sciences, Engineering, and Medicine states, 'There is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults' [13]. Nonetheless, a causative relationship between e-cigarette use and smoking initiation remains unclear. A 2019 analysis of youth tobacco trends challenge this assertion, citing an acceleration in the decline of past-30-day smoking after 2014 that coincides with a rise in youth vaping nationally [14]. However, it is unlikely that the reduction in cigarette use in the United States is because of the increase in e-cigarette use, especially since the decline in cigarette use among adolescents began in the 1990s, well before e-cigarettes came on the US market.

In adolescents, flavors, marketing, and lower perceived risk are thought to play a key role in initiation of vaping, due in large part to unfamiliarity with newer products and lack of prevention education. Adolescent responses in a 2015 survey-based study by Roditis *et al.* [15] embodied many common misperceptions about e-cigarettes, with some participants believing that aerosols from e-liquids are less addictive than traditional cigarettes and others stating that e-liquids do not contain any nicotine. In a 2018 study examining perceived health risks of pod-based devices, short-term and long-term health risks did not differ between pod-based and other e-cigarette devices [16]. However, risk perceptions among adults in two national surveys between 2012 and 2017 showed an increase in perceived harm, suggesting that risk perception will continue to improve over time [17].

NICOTINE DELIVERY AND MODERN DEVICES

An inherent problem in early vaping research arises from an evolving and largely heterogenous e-cigarette market. Although traditional cigarettes may contain small variations in nicotine content and packaging, combustible products are fairly homogenous. Vaping devices, on the other hand, have substantial differences in percentage nicotine content, formulation of nicotine (free-based vs. newer salt-based), e-liquid tank size, efficiency of nicotine delivery, device voltage, and other variables. Research continues to lag behind innovations in nicotine delivery. Although some products may contain a high concentration of nicotine, users may not achieve the same level of serum nicotine as they would from another device. Higher device voltage and alterations in solvent concentrations, for example, can produce drastically different aerosol delivery [18]. Such variations make research on dosage, nicotine concentration, addiction, perceived harm, flavors, and other factors extremely difficult.

A 2017 study found significant discrepancies in blood nicotine levels between different products among experienced e-cigarette users [19]. Blood nicotine levels in all e-cigarette products did not reach levels attained using combustible cigarettes; however, later generations of e-cigarette products such as Vuse and refillable e-cigarette brands resulted in significantly higher levels of serum nicotine when compared to first-generation ‘cig-a-likes’. The study suffered from large variations in vaping technique, user experience, and sample size. One study published in 2019 attempted to standardize vaping techniques between different devices and resulted in a similar pattern of greater serum concentrations after using advanced e-cigarettes when compared to first-generation devices [20]. A subsequent study by the same lead researchers showed greater and faster serum nicotine boosts in pod-based devices such as JUUL than both early generation cig-a-likes and advanced e-cigarette devices [21■■].

Pax Labs first received a US patent for its JUUL device in 2015 and has since overtaken its competitors as the dominant brand in the e-cigarette industry. The stated purpose of this patent was to allow for efficient plasma nicotine absorption while minimizing the harshness associated with inhalation of high concentrations of nicotine. By lowering the pH of e-liquids using a weak acid, users experience less bitterness allowing for nicotine concentrations 2–10 times greater than free-base nicotine contained in previous e-liquid formulations and resulting in greater plasma nicotine concentrations [22]. In addition to formula innovations, several elements of JUUL devices are attributed to their market dominance. Proprietary pods create a user-friendly experience as opposed to larger tank-based devices. They are also considerably smaller and easy to conceal. JUUL devices have the appearance of a USB flash drive. Design elements have drawn comparisons to popular tech products and has been referred to as the ‘iPhone of e-cigs’ [23].

RESPIRATORY HARM OF E-CIGARETTES

Most modern e-liquids contain three components: nicotine, a solvent, and a chemical flavorant. E-liquid solvents contain a propylene glycol and vegetable glycerin that determine properties of aerosolization based on the ratio of these components. Debate exists regarding the specific danger posed by solvents alone. Early studies of these components described propylene glycol as well tolerated when ingested; however, findings suggest that propylene glycol causes oral and nasal irritation, and minimal squamous cell metaplasia [24]. More recent studies have revealed potentially toxic effects in human cells [25].

Nicotine has long been known to have serious adverse effects to virtually every organ system, but can result in specific harm to lungs when inhaled [26]. Upon exposure to nicotine, parasympathetic ganglia are stimulated, causing bronchoconstriction and resulting in increased airway resistance in a dose-dependent manner and dysregulates central nervous system control of breathing through stimulation of nicotinic acetylcholine receptors [27]. Over time, nicotine can result in changes similar to chronic obstructive pulmonary disease by decreasing elastin and increasing volume of alveoli [26]. Similar findings were demonstrated in a 2016 study examining the effects of nicotine-containing e-liquids in the lung tissue of mice and humans. Pulmonary function testing of nicotine-exposed mice showed a FEF_{50}/FVC ratio reduction from 23 to 15, suggesting small airway obstruction. Lung parenchyma analysis revealed morphology similar to emphysema with significant reduction in alveolar surface area and increase in alveolar volume [28].

Immune function may be significantly altered as well. Exposure to e-liquids has been shown to cause immunologic changes, resulting in significant derangements of the inflammasome, elevated macrophage numbers, and increased Caspase expression resulting in apoptosis [28,29,30■]. Direct mucociliary dysfunction has been demonstrated through a variety of mechanisms in both *in vitro* and *in vivo* models [30■], and nicotine-containing e-liquids have been shown to reduce ciliary beat frequency in human lung epithelial cells [28]. Aerosolized e-liquids result in acquired cystic fibrosis transmembrane conductance regulator dysfunction, indirectly impairing mucociliary clearance similar to combustible tobacco exposure [31■,32].

The physiologic effects of flavors are highly variable given the enormous variety of available flavors in e-liquids. Artificial flavors can be chemically synthesized to replicate pleasing aromas or can be extracted directly from source components and thus properties of individual flavors determine specific toxicity to humans. Components in flavoring ingredients implicated to be harmful in humans include diacetyl and acetylpropionyl, which have been associated with toxic damage resulting in bronchiolitis obliterans [33]. Alpha-diketones have been shown in rodent studies to cause bronchial fibrosis with direct exposure [34]. It is important to note, however, that concentrations of these chemicals vary greatly depending on the flavorant itself and the method of synthesis or extraction, which can have drastically different effects on human lung tissue.

A 2018 study by Muthumalage *et al.* examined oxidative stress and inflammatory effects of common flavoring chemicals including acetoin, diacetyl, pentanedione, cinnamaldehyde, maltol, ortho-vanillin, and coumarin at various concentrations. Among these, cinnamaldehyde showed the greatest cytotoxic effect, although ortho-vanillin, pentanedione, and menthol derivatives also showed significant cytotoxicity. Expression of proinflammatory cytokine, Interleukin 8, known to play an important role the pathogenesis of cancer, was significantly increased when exposed to diacetyl, pentanedione, o-vanillin, maltol, coumarin, and cinnamaldehyde [35]. Cinnamaldehyde has been correlated with severe cytotoxicity in numerous other studies [25,36,37].

Long-term studies present a challenge in vaping research because of the relative novelty and evoling nature of these products. However, a 2019 longitudinal analysis examined the association of chronic respiratory disease (chronic obstructive pulmonary disease, chronic bronchitis, emphysema, or asthma) with e-cigarette use [38]. When controlled for combustible tobacco smoking, current e-cigarette use was associated with incidence of respiratory disease by a factor of a 1.29. This is among the first population-based longitudinal studies on the long-term harms of chronic e-cigarette use.

E-CIGARETTE OR VAPING PRODUCT USE-ASSOCIATED LUNG INJURY

Although not directly linked to commercial e-cigarette use, the recent epidemic of vaping-related illnesses merits discussion as it has brought e-cigarette use in adolescents to unprecedented levels of national attention. The e-cigarette or vaping product use-associated lung injury (EVALI) epidemic began in mid-2019 under mysterious circumstances, with seemingly random occurrences of acute respiratory failure in patients reporting recent vaping. By the end of 2019, more than 2500 EVALI cases had been reported from all 50 states, Washington, DC, Puerto Rico, and the US Virgin Islands, with 55 reported deaths [39■]. Analysis of bronchial alveolar lavage fluid samples from 51 EVALI case patients revealed the presence of vitamin E-acetate in 94% of the samples [40]. Vitamin-E acetate is used as a diluent in THC-containing e-liquids sold primarily through illicit markets. To our knowledge, vitamin-E acetate is not a common ingredient or diluent in nonillicit commercially available e-liquids; however, more investigation is needed to verify this, and tests on the remaining samples from the remaining patients is sorely needed. Nonetheless, it is important to make the distinction between acute lung injury from illicit devices containing potentially fatal chemical adulterants and devices that pose a more insidious threat of nicotine addiction and long-term lung damage.

CONCLUSION: POPULATION-BASED BENEFITS VERSUS RISK

There now exists a divide between the potential risk of generation-wide nicotine addiction and the potential benefit of smoking cessation. A 2018 report by Public Health England (PHE) maintained that ‘vaping is at least 95% less harmful than smoking [cigarettes]’. Yet as recently as 2019, an update by PHE emphasizes risk reduction in adult smokers, while acknowledging the potential for youth initiation of e-cigarette [41,42]. This is in stark contrast to a 2019 report by the European Respiratory Society, that states ‘long-term effects of ECIG use are unknown, and there is therefore no evidence that ECIGs are safer than tobacco in the long term. Based on current knowledge, negative health effects cannot be ruled out [43].’ US organizations with vested interest in e-cigarette policy and youth lung health including the American Thoracic Society, the Centers for Disease Control and Prevention, the American Lung Association, and the American Association of Pediatrics, recommend alternative smoking cessation tools and advocate for tighter regulations and age restrictions for the purchase of e-cigarettes [44,45■,46,47].

In recent years, a flood of data have emerged on nicotine-containing e-cigarette devices and their potential for respiratory harm and addiction. Much of the controversy surrounding e-cigarettes in adolescents stems from its relationship to traditional tobacco. Epidemiologic data in adolescents show a significant rise in e-cigarette use with concurrent decline in cigarette smoking within the past decade, however the decline in cigarette use started long before e-cigarettes entered the US market [2■■]. Further, the rate of rise in e-cigarette use among adolescents has far exceeded the already-low rate of traditional tobacco use. It stands to reason that the vast majority of adolescents in the present day would have never used combustible cigarettes, and thus comparisons of relative risk between the two products is not nearly as relevant to this population. Far more relevant is the observation that millions of adolescents are becoming addicted to nicotine at an unprecedented rate, using devices engineered to deliver aerosols with increasing efficiency, and undergoing a worldwide experiment in which the long-term effects are unknown.

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KEY POINTS

- Nicotine addiction among adolescents has experienced an unprecedented rise in the past decade due in large part to the emergence of electronic nicotine delivery systems known as e-cigarettes.
- The rise in e-cigarette use has been attributed to numerous factors including small, sleek devices, technological advances in nicotine-salt formulations, and attractive flavors.
- Respiratory harms associated with e-cigarette include changes to the inflammasome, delayed mucociliary clearance, impaired pulmonary function, and histologic alterations to the alveoli.
- Although there are conflicting data on the efficacy of e-cigarettes as a smoking cessation tool, there is increasing evidence that inhalation of aerosolized e-liquids may have detrimental effects on lung health. Public misperception of harm plays a large role in increased use of e-cigarettes among youth.