Electronic Cigarettes: A Pro–Con Review of the Current Literature

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Electronic cigarettes (e-cigarettes, e-cigs, or electronic nicotine delivery systems) are battery-operated devices typically containing glycerol and/or propylene glycol-based solutions with varying nicotine content, known as e-liquids. Although e-cigarettes were originally developed as a potentially less harmful alternative to traditional combustible tobacco cigarette smokers, several factors have driven their popularity among smokers and nonsmokers alike, including their sleek product designs, innumerable appealing flavors, lack of combustible smoke and odor, and high potential nicotine concentrations. Furthermore, many advocates have promoted the idea that e-cigarettes are safe to use, or at least safer than conventional tobacco, despite limited longitudinal data to support these claims. Here, we examine what is known about the impacts of e-cigarette use on traditional cigarette smoking cessation, lung health, and youth and young adult tobacco product exposure. Upon review of the currently available literature, the negative effects of e-cigarette use seem to outweigh any potential benefit, because the available evidence does not confirm the use of e-cigarettes as an effective strategy for supporting traditional combustible tobacco cigarette smoking cessation, particularly given the emerging adverse effects on lung health and the potential future public health effects of e-cigarette adoption among a burgeoning new generation of tobacco product users. **(J Allergy Clin Immunol Pract 2022;10:2843-51)**

Key words: E-cigarette; Nicotine; Smoking cessation; EVALI; Dual use

INTRODUCTION

Electronic cigarettes (also known as e-cigarettes, e-cigs, or electronic nicotine delivery systems [ENDS]) are battery-operated nicotine delivery devices typically filled with glycerol and propylene glycol-based solutions with varying nicotine content, known as e-liquids.[1,2] Although e-cigarettes were historically developed to supplant traditional combustible tobacco use with a less harmful alternative, several factors have driven e-cigarette popularity, including their many appealing flavors, the lack of combustible smoke and odor, sleek profiles, and high potential nicotine concentrations. Furthermore, many consumers and advocates have promoted the idea that e-cigarettes are safe to use, or at least safer than conventional tobacco. However, limited longitudinal data exist to support those suppositions, given the relatively recent emergence of e-cigarettes as a prominent tobacco product. Here, we examine what is known about the impacts of e-cigarette use on traditional cigarette smoking cessation, lung health, and youth and young adult tobacco product exposure.

ELECTRONIC CIGARETTE USE AND SMOKING CESSATION

Development and current use

The earliest patent for an e-cigarette was granted in August 1965 to Herbert A. Gilbert (US Patent No. 3,200,819),[3] who designed a "smokeless nontobacco cigarette" with multiple flavor options yet without nicotine, with the intent of replacing the combustible tobacco cigarette with a safer, less harmful alternative.[4] However, in focus groups run by tobacco companies, smokers did not find the aerosol produced by Gilbert's device appealing, likely because of the absence of nicotine and the subsequent inability to activate the dopamine reward system. The device never made it to market.

In the mid-2000s, the modern e-cigarette was invented and use skyrocketed in popularity in the United States and Europe, especially among youths and young adults. Some factors driving the popularity of these products include the availability of thousands of flavors allowing for a personalized product selection,[5,6] minimal regulation by the government resulting in the perception of their being less harmful than combustible tobacco products,[7,8] and extensive marketing by manufacturers as smoking cessation aids.[9] However, to date, no clear consensus

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has emerged regarding the utility of e-cigarettes for smoking cessation, and e-cigarettes have not been approved by the Food and Drug Administration (FDA) Center for Drug Evaluation and Research for this purpose. Although several randomized controlled trials and observational studies have been conducted during the past decade to address this specific question, many earlier studies did not include control groups, used early-generation e-cigarette types with poor nicotine delivery, or were inconclusive owing to the small sample size or challenges in the study design.

E-cigarettes as smoking cessation aids

Short-term studies (less than 1 year) published to address the efficacy of e-cigarettes as smoking cessation aids have yielded dichotomous results.[10-13] A 2021 Cochrane analysis evaluated the effect of e-cigarette consumer product use on smoking cessation and found that in all adult smokers (odds ratio [OR] = 0.947; 95% CI, 0.772-1.1600) and smokers motivated to quit smoking (OR = 0.851; 95% CI, 0.684-1.057), e-cigarette consumer product use was not significantly associated with a higher quit rate.[14] In contrast, quit rates were higher in cigarette smokers who used e-cigarettes daily (OR= 1.529; 95% CI, 1.158-2.019) relative to smokers who use e-cigarettes less than daily (OR= 0.514; 95% CI, 0.402-0.665).[11,14] When prescribed as smoking cessation aids and administered free of cost in randomized control trials, e-cigarettes offer little benefit over usual care or no treatment.[10,12]

Furthermore, in the longest observational study performed to date, Flacco et al[11] found no evidence that e-cigarette use increased smoking cessation rates over a 6-year period (2013-2019), nor was there evidence of harm reduction in e-cigarette or dual users (those using both e-cigarettes and combustible cigarettes) compared with cigarette smokers. Abstinence from combustible tobacco use was assessed with exhaled carbon monoxide testing in 228 e-cigarette users (all ex-smokers), 469 cigarette smokers, and 215 dual users. Among e-cigarette users, 64.0% remained tobacco abstinent. Tobacco cessation rates were equivalent in both dual users and tobacco smokers (38.6% vs 33.9%), respectively. The authors found that although the switch from combustible cigarettes to e-cigarettes supported abstinence from conventional cigarette use, the continued used of e-cigarettes in addition to smoking cigarettes did not improve smoking cessation or reduction.[11]

E-cigarettes and the harm reduction principle

Harm reduction via e-cigarette use has also been evaluated by measuring tobacco-specific toxicants and carcinogens. Like cigarettes, aerosols from e-cigarettes have been found to contain nicotine, nitrosamines, carbonyl compounds, heavy metals, and particulate matter.[12,13,15] Although present in smaller quantities compared with combustible tobacco products, these chemicals are well-known for their addictive nature and toxicity.[16,17] In the national cohort Population Assessment of Tobacco and Health (PATH) study including 3,211 participants consisting of exclusive cigarette smokers (79.7%), exclusive e-cigarette users (5.3%), and dual users (15.0%) from waves 1 and 2, five urinary biomarkers were examined using multivariable regression models: (1) nicotine metabolites and minor tobacco alkaloids, (2) tobacco-specific nitrosamines, (3) metals (heavy metals and speciated arsenic), (4) polycyclic aromatic hydrocarbons, and (5) volatile organic compounds. Switching from exclusive cigarette use to exclusive e-cigarette use (1.2%) resulted in a decreased urinary toxicant content; however, most participants maintained exclusive e-cigarette use or became dual users of combustible cigarettes and e-cigarettes. In these individuals, levels of urinary toxicants did not decrease.[18] Most dual users maintained dual-use status (37.9%) or transitioned back to exclusive combustible cigarette use (49.1%) 1 year later. The authors concluded that e-cigarettes tended to be used as supplements to conventional cigarettes, resulting in dual use and reduced efficacy as smoking cessation aids.

E-cigarettes and nicotine replacement therapy

Treatment with nicotine replacement therapy (NRT) and combination therapies for smoking cessation achieves abstinence rates of approximately 26% at 6 months and 20% at 1 year.[19-21] Compared with traditional NRT, epidemiologic studies show that e-cigarettes can be more effective than NRT alone in achieving smoking cessation. Walker and colleagues[22] examined the effects of dual NRT using nicotine patches and nicotine-containing e-cigarettes compared with nicotine patches alone and nicotine-free e-cigarettes. Unfortunately, a control cohort using e-cigarettes alone was not included in the study design. Exhaled carbon monoxide was used to verify continuous combustible tobacco abstinence at 6 months. Participants in the nicotine patches and nicotine e-cigarette group had a modestly higher quit rate (7%) than those in the nicotine patches and nicotine-free e-cigarette group (4%) (risk difference = 2.99; 95% CI, 0.17-5.81).[22] The group treated with nicotine patches and nicotine e-cigarettes received higher total nicotine replacement levels compared with the patches-alone group, which may explain the slightly higher abstinence rate, such that the role of the specific nicotine delivery system was not directly assessed in this study. The quit rate in the nicotine patches-alone groups was 2% (risk difference = 4.60; 95% CI, 1.11-8.09), which is extremely low compared with similar NRT studies. This raises concerns regarding the study design and the presence of extra-treatment factors that adversely influenced NRT.[21]

The finding that e-cigarettes are superior to NRT in achieving smoking cessation was also noted in a 2019 study in which 886 adult smokers were randomly assigned to receive either NRT (n = 447) or a nicotine-containing e-cigarette starter pack (n = 439). In this study, participants also received weekly face-to-face counseling for 1 year. The primary outcome was sustained smoking abstinence at 52 weeks. The authors found that 18% of participants who used e-cigarettes for smoking cessation aids were no longer smoking conventional tobacco a year later compared with 9.9% of participants who used NRT to quit smoking (relative risk = 1.83; 95% CI, 1.30-2.58; $P < .001$).[23] However, among e-cigarette users, 80% (63/79) were still vaping a year later (and thus using a tobacco product), compared with only 9% of participants in the NRT group still using NRT (four of 44), and 110 participants in the e-cigarette group (25%) had become dual users.[23] Although these findings suggest that e-cigarettes may be helpful for traditional tobacco cigarette cessation in smokers, they also highlight the potential for new sustained dependency and use of e-cigarettes when used for this purpose among former smokers.

E-cigarettes and addictive potential

The addictive potential of e-cigarettes was evaluated in another 2019 study using the Fagerstrom test for nicotine dependence, a 25-item questionnaire modified to analyze nicotine dependence and patterns and attitudes toward using e-cigarettes and combustible cigarettes.[24] Thirty e-cigarette users, 30 smokers, and 30 dual users were evaluated. Habits and behaviors associated with using e-cigarettes did not differ significantly between exclusive e-cigarette users and dual users. Surprisingly, nicotine dependence as measured using the Fagerstrom test for nicotine dependence was twice as high in e-cigarette users (mean, 3.5) compared with traditional cigarette smokers (mean, 1.6; $P < .001$),[25] affirming that e-cigarettes can be powerful activators of nicotine addiction pathways in the brain, and that using these devices can convey an addictive potential similar to conventional tobacco products.

Equally disturbing are further data from the PATH cohort study examining the addictive potential of e-cigarettes in 2,273 adult former tobacco smokers from waves 1 to 4 (2013-2018). Adult former smokers who reported using e-cigarettes after wave 1 and who had not used traditional cigarettes during wave 1 of the PATH trial were found to be at increased risk for traditional cigarette smoking relapse (adjusted hazard ratio = 1.63; 95% CI, 1.04-2.53 in recent former smokers; unweighted n = 304, and adjusted hazard ratio = 3.79; 95% CI, 1.75-8.20; unweighted n = 1,554 in long-term former smokers).[26]

A separate analysis of 26,446 adults completing two waves of PATH (2013-2014 and 2014-2015) also showed that e-cigarette use increased rates of new combustible tobacco product use in adults, compared with adults who had never used e-cigarettes ($P < .001$). Adults who had never used e-cigarettes at baseline but reported ever trying e-cigarettes were four times as likely to have transitioned to ever smoking combustible cigarettes than never smokers who had not used e-cigarettes (OR = 4.0; 95% CI, 2.6-6.1). Adults who used e-cigarettes in the past 30 days were six times as likely to have transitioned from never to ever combustible cigarette smokers (OR = 6.6; 95% CI, 3.7- 11.8) and eight times more likely to have become established combustible cigarette smokers (OR = 8.0; 95% CI, 2.8-22.7) than those who had never used e-cigarettes. These studies emphasize the importance of discouraging e-cigarette use in former smokers who had successfully quit smoking, and of advising never-smokers against initiating use.[27]

Finally, Beard and colleagues[28] examined how far changes in the prevalence of e-cigarette and licensed NRT use while smoking were accompanied by changes in cigarette consumption at the population level in active cigarette smokers. This observational study performed in England between 2006 and 2016 showed no statistically significant associations between changes in e-cigarette use ($\beta = -0.012$; 95% CI, -0.026 to 0.002) or NRT use ($\beta = 0.015$; 95% CI, -0.026 to 0.055) and daily cigarette consumption.[28]

Taken together, although some studies have shown that e-cigarette use may lead to short-term smoking cessation, they represent an inferior treatment approach relative to well-proven smoking cessation strategies, and their addictive potential combined with the lack of proven harm reduction supports caution against their use for smoking cessation.

TABLE I. Reported effects of electronic cigarettes on lung health

Human reports	Animal studies
Acute lung injury/ electronic cigarette or vaping product use-associated lung injury	Airway hyperreactivity/ bronchospasm
Acute respiratory distress syndrome	Altered immune cell function
Altered immune cell function	Altered gene expression
Altered epithelial cell function	Cellular cytotoxicity
Altered epithelial cell protein and gene expression	DNA strand breaks
Alveolar hemorrhage	Emphysema
Asthma and chronic obstructive pulmonary disease exacerbations/ increased symptomatology	Increased MUC5AC mucin/ goblet cell metaplasia
Bronchiolitis	Increased susceptibility to infection
Bronchitis/productive bronchitis	Increased susceptibility to acute respiratory distress syndrome
Cough	Inhibition of ciliary beating
Eosinophilic pneumonia	Nasal squamous metaplasia
Hypersensitivity pneumonitis	Oxidative stress
Increased MUC5AC mucin	Pulmonary fibrosis
Lipoid pneumonia	Tumorigenesis
Organizing pneumonia	
Shortness of breath	
Wheezing	

ELECTRONIC CIGARETTE USE AND LUNG DISEASE

Whereas we have had over 140 years to witness lung diseases caused by conventional tobacco, we have had less than 20 years to identify and classify lung diseases associated with e-cigarette use. In addition, we have only recently begun regularly asking patients about and documenting e-cigarette use in medical records. As such, data are limited and often rely on animal studies, case reports, series, and cohorts describing associated lung effects and symptomatology. Table I lists some of the reported lung health effects of e-cigarette use in both human and animal studies.

Cytotoxic effects

Whereas e-cigarettes have not been around long enough to determine whether consistent use leads to common tobacco product−related lung diseases such as emphysema, chronic bronchitis, interstitial lung diseases, or lung cancer, *in vitro* and *in vivo* studies using animal models have consistently found toxic and procarcinogenic effects of e-cigarette aerosols. One of the first studies, by Yu et al,[29] found that exposure to e-cigarette aerosols led to DNA strand breaks and cytotoxicity across cell lines. Notably, this cellular and molecular damage known to drive tumorigenesis was independent of nicotine. Since that publication in 2016, several groups have identified further DNA damaging and DNA-repair limiting effects of e-cigarettes,[30-32] as well as direct cytotoxic[30,33-36] and carcinogenic[31,37] effects of e-cigarettes.

Cellular immunomodulation

Immune cells, which are important pathologically across lung diseases such as pneumonia, interstitial lung disease, asthma, and cancer, have been found to be phenotypically and functionally altered and immunomodulated by e-cigarette aerosols and their components. This is particularly concerning in the setting of infection, because the diminished ability of host defense cells to clear pathogens (bacteria, viral, and fungal) predicts that e-cigarette users may have higher rates and higher severity of infectious diseases. Through murine studies, data in this area have emerged in both airway and lung parenchymal immune cells,[38,39] raising concern regarding increased susceptibility to pneumonia, as well as in circulating immune cells and those within distant organs (heart and colon), potentially increasing susceptibility to bacteremia, sepsis, and multiple-organ failure in the setting of an infectious challenge. Nevertheless, further studies are needed to ensure these findings are similarly borne out in human cells with typical e-cigarette product use.

Accordingly, some of the most common questions during the COVID-19 epidemic were whether e-cigarette use increased the risk for being infected with SARS-CoV-2 and whether vaping increased severity and mortality. Although these questions have not yet been answered to our satisfaction in human subjects, the data are most supportive of e-cigarette users having more respiratory symptoms even before viral infections,[40-43] with potentially increased symptoms in the setting of COVID-19.[44] One national cross-sectional survey of adolescents and young adults (aged 13-24 years) performed in May 2020 found that both e-cigarette users and dual e-cigarette and cigarette users were more likely to receive a diagnosis of COVID-19 compared with nonusers, and ever-users of e-cigarettes were five times more likely to test positive (OR = 5.05; 95% CI, 1.82-13.96),[45] although the authors noted that there were likely both immunologic and social contributors to positive testing among e-cigarette-using young adults. There are no convincing data that e-cigarette use leads to greater disease severity or higher mortality in COVID-19.[46,47] However, murine and *in vitro* data suggest that daily e-cigarette use leads to increased angiotensin converting enzyme-2 expression[48-50] and is associated with more severe acute lung injury in the setting of viral infections, including a murine coronavirus and influenza virus.[51,52] Thus, the current conclusion is that e-cigarette use likely leads to altered inflammatory responses in the lungs, which potentially will influence disease severity in some viral lung infections.

Data on immunophenotype changes induced in innate immune cells, both present in the lungs at baseline and recruited during inflammatory and infectious challenges, can be insightful as to why e-cigarette use may lead to altered inflammatory responses in the lungs. Human alveolar macrophages and murine bone marrow–derived macrophages exposed to e-cigarette aerosols have decreased phagocytosis and efferocytosis.[33,53] Human macrophages differentiated from the monocytic THP-1 cell line exposed to multiple common components of e-liquids (nicotine, propylene glycol, glycerol, and numerous flavorants) show diminished phagocytosis of bacteria after nicotine or flavor exposure, and diminished inflammatory cytokine secretion after exposure to any e-liquid component, including flavors.[54] Neutrophils from the circulation of e-cigarette aerosols as well as those exposed to e-cigarette aerosol extracts were found to have altered neutrophil extracellular trap formation and diminished antimicrobial function.[55] Epithelial cells, which themselves have multiple antimicrobial and inflammatory functions, demonstrate increased permeability and diminished signaling for help after e-cigarette exposure.[56] This combination of functional and phenotypic changes across macrophages, neutrophils, and epithelial cells suggests that e-cigarette use affects the innate immune system, reducing functional abilities to response to infectious challenges.

Potential for clinical disease development

Murine models are one of our only tools with which to determine whether e-cigarette use may cause disease over time, because exposure of mice to e-cigarette aerosols for months is the equivalent of years to decades in humans.[57] Broadly, murine models have demonstrated that emphysema can occur owing to e-cigarettes, but it may be a factor of both genetics and exposure,[58-60] and that pulmonary fibrosis may be promoted by using e-cigarettes.[60] In addition, multiple groups have shown diminished host responses to infectious challenges in the setting of e-cigarette aerosol inhalation (bacterial and viral),[51,55] and increased pathogen virulence (bacterial and fungal).[35,61] One of the most shocking studies of 2019 was the article by Tang et al,[37] which demonstrated an increase in lung adenocarcinoma tumorigenesis in the setting of a year of daily e-cigarette aerosol exposure, depending on the presence of nicotine within the aerosols. Finally, e-cigarette exposure daily for months has been shown to cause disease beyond the lung, including cardiac, renal, and hepatic fibrosis, neuroinflammation in the central nervous system, and altered inflammatory states in the heart and colon.[56,62]

Although much is still unknown, there are multiple reports identifying e-cigarette use as the cause of a variety of more acute and subacute lung diseases, including eosinophilic pneumonia,[63] hypersensitivity pneumonitis,[64,65] bronchiolitis,[66] organizing pneumonia,[67] alveolar hemorrhage,[68,69] and acute respiratory distress syndrome. In many of these cases, patients became critically ill before clinicians could recognize or identify the inhalant use as a potential driver. Thus, these few cases that were identified as related to e-cigarettes suggest that many more may be occurring across the world but are not being identified as related to vaping.

The e-cigarette or vaping product use-associated lung injury epidemic

In 2019, a lung disease specific to vaping of tetrahydrocannabinol (THC) was identified: e-cigarette or vaping product use-associated lung injury.[70,71] Many of the affected patients were teenagers or young adults, and some required our highest level of support, extracorporeal membrane oxygenation.[65,66,72] Whereas the e-cigarette or vaping product use-associated lung injury epidemic is a disease of THC vapers (cases have continued to be identified into 2022), this epidemic brought to light the dangers of inhaling chemicals that have never been assessed for potential pulmonary (and whole-body) toxicity. It took over 60 deaths and thousands of vapers falling ill before vitamin E acetate was identified as the causal agent, which was being added to THC containing e-liquids by retailers. Of note, vitamin E does not sound dangerous, and liquid formulations are widely available in stores and online. Many people ingest it or apply it topically, because it is generally considered safe for consumer use. Thus, it came as a surprise to many to find that it was highly toxic to lung cells when inhaled. Because there has been no regulation of what chemicals can and cannot be added to nicotine or THC e-liquids, it may be only a matter of time until the next lung injury epidemic owing to vaping devices occurs.

Secondhand vapor exposure

One area in which the theoretical potential for e-cigarette—related harm reduction has been proposed is in secondhand smoke (SHS) exposures. It is well-documented that secondhand smoke exposure leads to suppressed lung development in children and increased development of obstructive lung disease, and promotes the development of lung cancer in otherwise nonsmokers. Because e-cigarettes have been touted as healthier and safer than conventional tobacco, and because of the less averse smell and look of e-cigarette aerosols compared with conventional tobacco smoke, many parents who switched to e-cigarettes began vaping in their homes and cars in the presence of their children. This has led to high secondhand e-cigarette aerosol exposures in those who live with e-cigarette users. However, we now have data demonstrating that lung diseases and respiratory symptoms are occurring as the result of secondhand e-cigarette aerosol exposure.[73] Galiatsatos et al[74] identified a case of hypersensitivity pneumonitis resulting from secondhand e-cigarette aerosol exposure, whereas Alnajem et al[73] showed an increase in wheeze and asthma. Accordingly, secondhand e-cigarette exposure may not be as innocuous as previously considered, and further studies are needed to explore the potential future implications of e-cigarette use on lung health.

ELECTRONIC CIAGARETTE USE AMONG ADOLESCENTS AND YOUNG ADULTS

The past decade has seen a sharp rise in the use of e-cigarettes and vaping devices globally among youth and young adults. E-cigarettes have become firmly established as the most commonly used tobacco product among youth in the United States since 2014.[75,76] In 2020, nearly one in five high school students (19.6%) reported currently using e-cigarettes.[75,77] The ongoing adoption of e-cigarettes among America's youth has garnered significant recent attention from public health advocates, because their uptake has dampened efforts to combat tobacco product use among adolescents. E-cigarette popularity is to blame for the concerning plateau in the use of tobacco products among high school students. More than one in four high school students (26.3%) continue to report current use of tobacco products.[75,77]

Potential for relative harm reduction in youth tobacco product use

Some authors have proposed that this shift to using e-cigarettes among youths is a positive trend, arguing that this may represent a relative reduction in harm compared with the significant short- and long-term risks of traditional tobacco smoking. For example, in their cross-sectional matched control study, Shahab et al[78] used behavioral controls and propensity score matching within data between the 2014 and 2017 National Youth Tobacco Surveys to compare cigarette smoking rates of adolescents who first tried e-cigarettes compared with those who first tried cigarettes or more traditional tobacco products. They found that compared with adolescents who had tried a traditional cigarette as their first tobacco initiation product, adolescents who had used an e-cigarette first were less likely to be both past 30-day cigarette smokers (OR = 0.15; 95% CI, 0.12-0.18) and established cigarette smokers (OR = 0.04; 95% CI, 0.03-0.07). This suggests that youths who try e-cigarettes as their first tobacco product may be less likely to transition to traditional tobacco products in the future relative to those whose first tobacco product is conventional tobacco; less than 1% of young e-cigarette users in that study became established traditional cigarette smokers. Similarly, using data from the first three annual waves of the nationally representative sample of baseline tobacco-naive youths enrolled in the PATH study, Xu et al[79] found that the risk for past 30-day combustible cigarette use was comparatively sevenfold lower when youths started with an e-cigarette compared with a combustible cigarette. One hypothesis as to why using e-cigarettes first may lead to these youths and young adults sticking with e-cigarettes alone comes from Jankowski et al,[25] who found that nicotine dependence was two times greater in young (mean age, 22.4 years) e-cigarette users versus conventional cigarette smokers (mean age, 3.54 vs 1.64 years; $P < .001$). However, unlike in the study by Shahab et al, Xu et al importantly noted that among tobacco-naive youth in the PATH study, the initiation of e-cigarette use was associated with greater risk for subsequent initiation of combustible cigarette smoking (OR = 3.42; 95% CI, 9.68-68.72) as well as past 30-day combustible cigarette use (OR = 2.88; 95% CI, 1.22-6.86). However, this risk was higher when youths started with a combustible cigarette.[79]

Transition to traditional cigarette use

Unfortunately, numerous other prospective, longitudinal studies have demonstrated the strong association between the onset of youths' e-cigarette use and subsequent traditional cigarette smoking.[80-84] For example, in their longitudinal survey of high school students in southern California, Leventhal et al[80] found that even when adjusted for various sociodemographic, environmental, and intrapersonal factors including risk behaviors, baseline e-cigarette use was associated with a significant increase in the odds of traditional cigarette smoking in the similar range of 1.75 to 2.96 (OR), depending on the outcome. Furthermore, in a meta-analysis of nine US-based studies, Soneji et al[82] reported a concordant pooled OR for subsequent traditional cigarette smoking of 3.62 (95% CI, 2.42-5.41) for ever versus never e-cigarette users, after adjusting for known demographic, psychosocial, and behavioral risk factors for traditional cigarette smoking, with an even higher relative OR of 4.28 (95% CI, 2.52-7.27) among youths who reported e-cigarette use in the past 30 days.

Addictive potential and evolving e-cigarette technology

One recently published study comparatively evaluating data from the more recent PATH study waves 4 to 4.5 (years 2016-2018) and 4.5 to 5 (years 2017-2019) shows that whereas this strong association between ever e-cigarette use and subsequent transition to combustible cigarette smoking held in waves 1 to 3, an attenuation of the significance of this transition occurs in waves 4 to 4.5 (adjusted OR [aOR] = 1.40; 95% CI, 0.91-2.14) and in waves 4.5 to 5 (aOR = 1.35; 95% CI, 0.84-2.16),[85] despite the relatively high ongoing use of e-cigarettes as the current tobacco product of choice among youths in the United States.[77] One theory for this is that newer-generation e-cigarettes and ENDS for vaping are more efficient at nicotine delivery and may be supplanting the need for traditional combustible cigarette use to obtain a greater high once dependence has occurred.[86,87] Historically traditional combustible cigarettes have allowed for the fastest and most efficient delivery of nicotine among the array of available tobacco products,[79,86,88] reinforcing their status as some of the most addictive products sold on commercial markets. However, the more recent advent of customizable Pod Mod devices coupled with innovations in nicotine chemistry allow for the use of less caustic protonated nicotine formulations derived from the nicotine salts in loose-leaf tobacco as well as perhaps even more appealing, completely synthetic nicotine salts. Thus, newer-generation e-cigarettes and ENDS are now able to deliver much higher nicotine concentrations than combustible cigarettes without the traditional acerbic taste and inhalational effects commonly associated with combustible cigarettes.[86,87,89-92] These devices have additional appeal among youths because they often have sleek, easily concealed designs resembling pens or USB devices or are even made to resemble smartphones, gaming devices, and popular cartoon characters.[86,87,93] Furthermore, newer-generation salt-based nicotine e-liquids are available in a host of attractive fruity, minty, and candy-based flavors that hold appeal for youthful users, which can further mask subjective caustic initial effects of higher-dose nicotine inhalation,[86,87,94] are associated with an increased odds of adolescent vaping continuation (aOR = 3.76; 95% CI, 1.20-10.31) and a higher level of nicotine-containing puffs taken on each vaping event (mean, 3.1 ± 5.5 vs 1.5 ± 3.8), compared with the use of unflavored tobacco or menthol flavors among youths who use e-cigarettes.[94] Data from the most recent 2021 NYTS revealed that among youths currently using e-cigarettes, the most commonly used device type was disposables. Both high school and middle school students reported that their usual brand of choice was Puff Bar (Puff Bar, Wilmington, DE; 26.1% and 30.3%, respectively),[75] a nicotinic salt–based product with flavors such as Guava Ice and Strawberry Banana. In fact, likely owing to this combination of reduced acridity, potentially higher nicotine content, and widely available range of flavors, all of the most recently reported top brands of choice favored among youths currently using e-cigarettes including Puff Bar, VUSE (R.J. Reynolds Vapor Company, Winston-Salem, NC), SMOK (Shenzhen IVPS Technology CO., Shenzhen, China), and JUUL (Altria Group, Richmond, VA),[75] offer nicotine salt–based products as top-selling products with increasing gains in sales market share.[95]

The use of these newer, rapidly absorbed, salt-based nicotine products and subsequent regular high-level exposure to nicotine among youths creates additional concern for public health officials because it is well-known that the developing adolescent brain is particularly susceptible to the effects of nicotine, which has been shown to influence long-term molecular, biochemical, and functional changes that increase the risk for future subsequent addictive behaviors, risk taking, and substance dependence.[89,96,97] Moreover, numerous studies have demonstrated the association between e-cigarette use among youths and other risk-taking behaviors including the use of alcohol and progression to other regular substance use including inhalational cannabis.[89,96-99] Furthermore, youths' exposure to nicotine via e-cigarettes is associated with increased risk for mood, attention, and sleep disorders.[86,91,97,100-102] Perhaps most concerningly, Kim et al[101] found that after adjusting for a variety of socioeconomic demographics, risk-taking behaviors, and reported stress levels, both male and female adolescents who used e-cigarettes had significantly higher rates of suicidal ideation, suicide planning, and actual suicide attempts than either traditional combustible cigarette users or never-smokers. The authors cited the possible contribution of higher peak level nicotine exposures, addiction rates, and withdrawal symptoms from the popular newer-generation nicotinic salt formulation e-cigarette and ENDS as a likely contributor to their findings. Concordantly, Zhang et al[103] found that among youths currently using e-cigarettes, 63.9% reported the desire to attempt to quit e-cigarette use, and that those reporting current nicotine dependency symptoms were more concerned about the e-cigarette use and more likely to have made a past-year attempt to quit (adjusted prevalence ratio = 1.17; 95% CI, 1.06-1.29). This underscores the need for a comprehensive approach to tobacco prevention and control among this new generation of youths for whom nicotine dependence is developing through even the sole use of e-cigarettes as the only tobacco product.

Regulation efforts and youths' access to e-cigarettes

Taken together, it is unsurprising that the evolving body of literature on the use of e-cigarettes among youths has caused a significant amount of consternation among those concerned with the health and well-being of adolescents and young adults. Calls have arisen for stronger regulatory actions in the e-cigarette and ENDS device markets.[75,77,86,87,104-106] In recent years, these calls have led to efforts at the federal level by the FDA to limit the sales of e-cigarettes to America's youth by increasing the federal minimum legal sales age for all tobacco products including e-cigarettes from 18 to 21 years across the United States.[104,107] The FDA also put forth a prioritized effort to regulate flavored, prefilled cartridge-based e-cigarettes as of 2020.[75,108] Perhaps owing to these efforts, data from the National Youth Tobacco Surveys demonstrated that current use of e-cigarettes declined for the first time in recent years between 2019 and 2020 among both high school (27.5% to 19.6%) and middle school students (10.5% to 4.7%).[77]

However, loopholes still exist in the ongoing development of flavored products and persistent pervasive marketing targeted at underaged e-cigarette users. Approximately 68% of US middle and high school students reported ongoing exposure to e-cigarette advertisements from both physical retail stores and Internet-based sources in 2020.[109] Furthermore, a recent survey among youths and young adults in California revealed that despite being under the legal age of 21 required for vaping device purchases in that state, most users (59.9%) reported being able to purchase their own devices both in person at vape shops and from online retailers.[92] Ongoing federal, state, and local efforts to prevent and reduce youth tobacco product use, including the use of e-cigarettes, will be imperative as the landscape of youth e-cigarette exposure continues to evolve.

CONCLUSION

Although e-cigarettes are a relatively new addition to the tobacco product market, their recent uptake among consumers, particularly among youths and young adults, warrants significant attention given the potential implications for both individual-level and population-based health outcomes. Currently, the negative effects of e-cigarette use seem to outweigh any potential benefit, because the available evidence does not confirm the use of e-cigarettes as an effective strategy for supporting traditional combustible tobacco cigarette smoking cessation, particularly owing to the emerging adverse effects on lung health and potential future public health effects of e-cigarette adoption among a burgeoning new generation of tobacco product users.

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