Health effects of electronic cigarettes

Judith Groner, MD

E-cigarettes cause harm to adolescent users. The devices and constituents create multiple substances which are toxic on inhalation, including nicotine, metallic nanoparticles, particulate matter, and carbonyls. In addition, there is a robust relationship between youth vaping and use of combustible cigarettes as adults. This finding is based on longitudinal research and is found among youth who were at low risk for use of combustible cigarettes. Therefore, the most substantially confirmed health hazard of youth vaping is creating a new generation of smokers of combustible cigarettes and the documented health risks of such use. The physiological and psychological harms of nicotine dependence during adolescence also have been well documented. Additionally, population-based research has shown a consistent link between current vaping and respiratory issues during adolescence itself. Significant lung disease (EVALI) has occurred in adolescents and not all cases are linked to vitamin E acetate. Finally, extrapolating research on adults to adolescents raises the possibility that e-cigarette use is linked to presymptomatic cardiovascular dysfunction and may have a significant health impact during adulthood. The combination of this evidence, from pre-clinical to population-based longitudinal studies, conclusively demonstrates that e-cigarettes are not safe for youth.

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Background

Electronic cigarettes (e-cigarettes) were introduced to the United States market from China in 2006[1] and have evolved rapidly from first generation cigarette lookalikes (cig-alikes) to modifiable tank style, then to pod mods such as JUUL, and finally to disposables.[2] These products have become popular with youth and young adults because of their styling, their perceived safety, desirable flavors, and the potential of using them discreetly.[2] The basic mechanism of all types of e-cigarettes is heat a solution to create an aerosol which commonly contains nicotine (although not always), a humectant (a substance to preserve moisture), and flavoring. All e-cigarettes have a mouthpiece, a sensor to activate a heating coil, a battery, a heating coil, and a reservoir for the liquid that is to be heated. The humectants commonly used are propylene glycol (PG) or vegetable glycerin (VG).

Mechanism of design and potential toxicity

Several mechanisms within the design of the e-cigarette itself may contribute to their potential toxicity. In tank-like devices in which the user can increase the resistance and adjust voltage, higher power levels have shown to result in the production of volatile carbonyl species such as formaldehyde, acetaldehyde and acrolein, and an increase of aerosol production.[3] Furthermore, the coils themselves are made of metals such nickel-chromium, chromium-aluminum-iron, but also may contain copper, silver, and tin. As these metals undergo repeated cycles of heating and cooling, traces of the metals may enter the e-liquid, causing the device to emit metallic nanoparticles found in the emissions.[4] Exposure to metal emissions in other settings is a known cause of increased respiratory tract infections and a risk of lung cancer.[5] Animal models of metallic emission exposure show lung injury and immune suppression.[6]

From the Nationwide Children's Hospital, Department of Pediatrics, The Ohio State University College of Medicine, Columbus, OH, USA.
E-mail: judith.groner@nationwidechildrens.org

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The humectants within the e-cigarettes as mentioned above are considered "Generally Recognized as Safe" (GRAS) for oral intake, but not for aerosolization. There is no research on long term inhalation of VG or PG. These are known to form toxic aldehydes when heated.[7] There are over 7500 flavorings that are commonly used in e-cigarette liquids designed to appeal to youth.[8] There is no evidence base to support that these flavorings can be safely inhaled. A known example is the toxicity of diacetyl, a buttery flavoring used often in microwave popcorn. Workplace inhalation exposure to diacetyl has been long associated with bronchiolitis obliterans.[9] Diacetyl has been found in many tested e-cigarette liquids despite this known association.[10] Flavorings in e-cigarette liquids in general are a main contributor toward the production of toxic carbonyl compounds.[11]

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Trajectory toward use of combustible cigarettes

The greatest potential long-term health effect of e-cigarettes on adolescents and young adults is the increased risk becoming a user of combustible cigarettes later in life with the concomitant health risks of regular smoking. This has been shown through multiple longitudinal studies.[12-17] It has been posited that this trajectory is merely that of high-risk youth who would have ended up becoming smokers anyway. However, the evidence is to the contrary. Youth who are at lower risk for use of combustible cigarettes as defined by three validated risk factors were at higher risk for initiating combustible cigarette use if they started with e-cigarettes.[16]

In a systemic review and metanalysis,[18] this risk was clearly demonstrated. The non-adjusted risk of initiation of combustible cigarette smoking for non-e-cigarette users was 7.2% compared to 23.2% for e-cigarette users.[18] Likewise, the rates of current past 30-day cigarette smoking were 4.6% for non-cigarette users versus 21.5% for e-cigarette users. After adjusting for known demographic, psychosocial and behavior risk factors for combustible cigarette use, the pooled odds for subsequent combustible cigarette initiation was 3.50 (95% CI, 2.38-5.16) for ever versus no e-cigarette use. Past 30-day cigarette smoking at follow up was 4.28 (95% CI, 2.52 − 7.27) for past 30-day e-cigarette use vs no past 30-day e- cigarette users at baseline.[18] Because this study controlled for known risk factors for cigarette smoking in the analysis, it is fair to conclude that e-cigarette use is an independent risk factor for the trajectory to combustible cigarette smoking. The transition to combustible cigarettes may be due to the hand to mouth behavior started with e-cigarette use, even if the e-cigarette did not contain nicotine. For those adolescents and young adults who use e-cigarettes that do contain nicotine, this use may be the pathway to nicotine addiction. E-cigarettes using protonated nicotine salts at high concentrations, such as Juul, deliver higher amounts of nicotine to user.[19]

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Nicotine dependence

Nicotine dependence and loss of autonomy have been demonstrated among youth who vape, particularly pod-based systems that deliver protonated nicotine at high levels.[20,21] Nicotine dependence is characterized by strong cravings, physiological withdrawal symptoms, continuing to vape to avoid withdrawal symptoms, and needing to vape more to be satisfied.[22] The loss of autonomy is the inability to stop using nicotine because of physiological or psychological sequelae to the quitting its use.[22] Preclinical and clinical studies alike have shown that

the adolescent brain is uniquely susceptible to the effects of nicotine.[23]

Pulmonary effects

Several large population-based studies in adolescents have noted increased asthma diagnoses, school absences due to asthma and respiratory symptoms for youth who currently use or have used e-cigarettes. A study from Korea with over 35,000 high school students examined the students' self-reported physician diagnosis of asthma in the past 12 months. Severity of asthma was assessed by days absent from school due to asthma symptoms. When adjusted for multiple confounders including past and current conventional cigarette smoking, the adjusted odds ratio (OR) for having an asthma diagnosis was 2.75 (95% CI 1.30 − 5.78).[24] Current e-cigarette users had the highest adjusted OR for severe asthma compared to never users of e-cigarettes [24] when analyzed by conventional cigarette current, past or never use, and days of school missed (four or more days or 3 days or less). For example, a current electronic cigarette user who never smoked conventional cigarettes had an OR of 15.42 (CI 5.11 − 46.57) for being absent from school for more than 4 days due to asthma.[24]

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Wang and colleagues examined the prevalence of respiratory symptoms (cough and phlegm for three months consecutively by self-report) in a group of over 45,000 high school students.[25] Among those who never smoked combustible cigarettes, vaping e-cigarettes was associated with an adjusted OR of 2.06 (1.24-3.42).[25] Within the U.S., researchers investigated associations between e-cigarette use and reported bronchitic symptoms (chronic cough, phlegm, or bronchitis) and of wheeze in the previous 12 months with over 2,000[26] Southern California Children's Health Study participants completing questionnaires in 11th and 12th grade in 2014.[26] Risk of bronchitic symptoms was increased by almost twofold among past users (odds ratio 1.85; 95% CI 1.37−2.49), compared with never-users, and by 2.02-fold (95% CI1.42−2.88) among current users. These associations however were weaker after adjustment for lifetime number of cigarettes smoked and second-hand smoke exposure. However, risk of bronchitic symptoms among past e-cigarette users remained elevated after adjustment for relevant potential confounders and was also observed among never−cigarette users (OR 1.70; 95% CI, 1.11−2.59.)[26]

EVALI

In July 2019, the Wisconsin and Illinois Departments of Public Health received reports of lung injury of unknown cause potentially associated with the use of vaping products. The new entity was called EVALI (Electronic cigarette or Vaping product use-Associated Lung Injury). The initial case series of 98 patients in Illinois and Wisconsin established a working definition of "respiratory failure with symptom onset within 90 days of electronic cigarette use, with pulmonary infiltrates on imaging, the absence of infection, and not evidence of alternate causes of respiratory failure."[27] The symptoms of EVALI are myriad and include respiratory symptoms such as shortness of breath, chest pain, cough, and hemoptysis (97%).[28] About one-third of reported EVALI patients require intubation and mechanical ventilation. Gastrointestinal symptoms are also common and include nausea, vomiting, and abdominal pain (77%), and 100% of patients had constitutional symptoms of fever and malaise. By December 2019 there were 2506 hospitalized cases in 50 states and the District of Columbia. [28]

Demographically, EVALI patients were young, with the median age 21 years, and 26% were younger than 18. They were predominantly male (79%), and most did not have a history of pulmonary disease except for asthma.[28] At presentation, over 80% had an abnormal chest x-ray[28] and of the ones who had CT scans, 100% were abnormal. Ground-glass opacities in both lungs were the characteristic CT finding.

All patients had a history of use of e-cigarettes within 90 days of symptom onset, and most (92%) had used an e-cigarette within a week of symptom onset.[28] Overall, over 80% reported using e-cigarette products containing tetrahydrocannabinol (THC). Nearly all (96%) THC-containing products reported were packaged, prefilled cartridges, and 89% were primarily acquired from informal sources (e.g., friends, family members, illicit dealers, or off the street).[29] A total of 27% of the patients reported using THC products only, whereas 11% reported using nicotine-

containing products only; 60% reported using both. A total of 60% of the patients reported using both nicotine and THC products. Patients reported using 27 distinct brands of THC products and 25 brands of nicotine products in a wide range of flavors. The most common THC product that was reported was marketed under the "Dank Vape" label used by 67% of patients interviewed.[28]

Analysis of bronchial-alveolar lavage (BAL fluids) showed that there was an association between Vitamin E acetate used as a thickening agent in THC products and development of EVALI.[27] However, despite the understanding that the THC agent was the usual culprit, there have remained approximately 10% of cases in patients who never used marijuana products.[30] According to the CDC the evidence is not strong enough to "rule out the contribution of other chemicals of concern, including chemicals in either THC or non-THC products, in some of the reported EVALI cases."[31] The EVALI epidemic appeared to have peaked in September 2019 and decreased by December 2019.[30] Since then, EVALI rates have continued to drop, which may be due to warnings about use of Vitamin E acetate in THC products and removal from some products. It is also possible that rates of EVALI are falsely low during the COVID-19 pandemic because diagnosis of EVALI may be delayed to due patients presenting with symptoms consistent with COVID-19.[32]

Cardiovascular effects

E-cigarettes have been shown to be associated with inflammation, oxidative stress, and hemodynamic imbalance, leading to increased risk of cardiovascular disease.[33] The research supporting this statement is derived from studies of young and older adults and has not been performed in adolescents. There is a research gap in studying the cardiovascular effects of these products during adolescence itself. In the absence of direct evidence of these issues in teens, it is important to be aware of what research has been done in adults.

Potential cardiotoxicity of e-cigarette constituents

Nicotine itself is known to induce a multitude of effects on the cardiovascular system.[33] It binds to nicotinic receptors which are in the autonomic ganglia and adrenal gland, resulting in the release of norepinephrine and epinephrine. This causes sympathetic nervous stimulation that can cause increased blood pressure.[33] In animal models, chronic sympathetic stimulation been shown to cause fibrosis of the heart with subsequent arrythmias and myocardial remodeling.[34]

Carbonyl compounds are found in e-cigarette vapor (formaldehyde, acetaldehyde and acrolein) and are the result of thermal decomposition of the humectants and some flavorings.[11,35] All of these compounds have been shown to have cardiovascular effects in pre-clinical studies.[33]

Particulate matter (both fine and ultrafine) are found in significant concentrations in e-cigarettes.[36,37] These can easily pass through the alveolar-endothelial border into the systemic circulation, directly affecting the heart, vascular and other organs. These have direct effects on the cardiovascular system through oxidative stress. Exposure to particulate matter has long been known to contribute to cardiovascular disease in the forms of atherosclerosis, thrombosis, coronary heart disease and hypertension.[33]

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Clinically, e-cigarette use has been associated with an increase in heart rate and blood pressure.[38,39] Originally these were much lower than those of combustible cigarettes because of the lower nicotine levels in the original e-cigarettes. However, with the introduction of tank-based cigarettes with higher voltages and lower resistance and protonated nicotine such as in Juul and disposables, blood nicotine levels in e-cigarette use are more similar to combustible use.[40] Recent studies therefore

have shown that acute e-cigarette use is associated with increased systolic and diastolic blood pressure and arterial stiffness, similar to combustible cigarettes.

Endothelial dysfunction

E-cigarette use is associated with endothelial dysfunction. The endothelium is a monolayer lining the entire cardiovascular system, and it is responsible for maintaining vascular tone and regulating oxidative stress by releasing mediators such as nitric oxide, prostacyclin, and endothelin. Endothelial dysfunction is a predictor of higher risk of cardiovascular disease. Repair of sites of endothelial injury relies heavily on arrival and incorporation of stem/progenitor cell type (s); cells defined as 'endothelial progenitor cells' (EPCs).[41] EPCs therefore play a role in vascular homeostasis and changes in EPC levels can be an early indicator of cardiovascular dysfunction. EPCs have been shown to increase one hour after acute e-cigarette vaping and return to baseline later,[42] indicating that the uptick in EPCs may be necessary for endothelial repair. Similarly flow mediated dilation (FMD), a known measure of vascular function which has been associated with future coronary artery disease, is impaired after use of e-cigarettes.[42] This implies endothelial function is impaired in response to the vaping episode.

Summary and conclusion

There are several streams of research that indicate health harms of e-cigarette usage for adolescents. First, the devices and constituents create multiple harmful substances that are toxic to inhale, such as nicotine, metallic nanoparticles, particulate matter, and carbonyls. Secondly, research has demonstrated a robust relationship between youth vaping and use of combustible cigarettes as adults. This finding is based on longitudinal research and is found among youth who were at low risk for use of combustible cigarettes. Therefore, the most substantially confirmed health hazard of youth vaping is creating a new generation of smokers of combustible cigarettes and the documented health risks of such use. The physiological and psychological harms of nicotine dependence during adolescence also have been well documented. Additionally, population-based research has shown a consistent link between current vaping and respiratory issues during adolescence. Significant lung disease (EVALI) has occurred in adolescents and not all cases are linked to vitamin E acetate. Finally, extrapolating research on adults to adolescents raises the possibility that e-cigarette use is linked to pre-symptomatic cardiovascular dysfunction that may have a significant health impact during adulthood. The combination of this evidence, from pre-clinical to population-based longitudinal studies, conclusively demonstrates that e-cigarettes are not safe for youth.

Declaration of Competing Interest

None.

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