E-cigarettes, Vaping, and the FDA’s Dilemma

Physician Focus Series
Introduction

In December 2018, US Surgeon General Jerome Adams took the extraordinary step of declaring a new epidemic among American youth: e-cigarette use.1 The word epidemic is never used lightly by a Surgeon General. Dr Adams' declaration was spurred by the publication, one month prior, of some startling new data that rang alarm bells throughout the FDA and CDC: e-cigarette use, which had already surpassed the use of combustible cigarettes among youth, increased by a whopping 78% among high-school students and 48% among middle-school students over a single year, from 2017 to 2018. During that year, 21% of high schoolers and 5% of middle schoolers admitted to current use of e-cigarettes.2 Another study reported over one-quarter (26.7%) of 12th graders use e-cigarettes. That translates to over 3.6 million teen e-cigarette users, an increase of 1.5 million students since 2017.³

While an eye-opener to many medical professionals not on the frontlines of caring for youth, these figures are likely not surprising to most students, teachers, and school administrators, who have seen “vaping” (the term used for inhaling an e-cigarette) become part of their daily landscape. The sudden spike in vaping among this age group, as well as among college-students, is attributed mostly to the introduction of JUUL, a specific brand of e-cigarette that is particularly popular with adolescents. The reasons for its popularity are myriad—more on that below. The ability to easily conceal the device is certainly a factor. Since the device resembles a typical USB flash drive, can be recharged when plugged into a laptop, and does not produce much of a telltale vapor trail during exhalation, it can be hidden in plain sight. In many schools, JUUL e-cigarettes are a ubiquitous (if surreptitious, as they are typically banned) presence in school cafeterias, restrooms, parking lots, and at athletic events. The device is so low profile that students can take quick hits almost anywhere. Many YouTube videos are available demonstrating how to “JUUL in school,” teaching such techniques as how to avoid detection by exhaling into clothing or swallowing the exhaled vapor plume.⁴ School administrators have reported that much of their time is now taken up with meting out disciplinary measures for students caught vaping in school.⁵
What are e-cigarettes, and what do they contain?

Battery-powered electronic nicotine delivery systems (ENDS) of various types have been available in the United States for about a decade but have only recently become popular, especially in the form of e-cigarettes. “Cig-a-likes,” the earliest iteration of e-cigarettes, closely resembled combustible cigarettes. Second-generation devices were often shaped like flashlights or pens (“vape pen”). More recent third-generation e-cigarettes come in a variety of shapes and sizes, including modular forms with refillable e-liquid tanks and customizable wattage (“mods”).

All e-cigarettes work in basically the same way. They include a battery, a heating coil, a reservoir or cartridge (sometimes known as a “pod”) of e-liquid, an atomizer that converts the heated e-liquid to an aerosol, and a mouthpiece from which to inhale the aerosol. Although the process of inhaling these heated ingredients is known as vaping, technically the process is aerosolization rather than vaporization. E-cigarettes are usually marketed as “vaping products” (or “vapes”) and the word “cigarette” is absent from advertising.

The devices are also sometimes used for vaping THC using cannabis-infused oils instead of nicotine e-liquids. E-liquids generally contain nicotine, derived from tobacco, although some e-liquids are available in nicotine-free versions. The nicotine content of e-liquids varies widely and comparison across products can be difficult. In general, a pod of e-liquid inhaled via a JUUL e-cigarette approximates the amount of nicotine in a pack of combustible cigarettes.

In addition to nicotine, e-liquid contains flavorings mixed with a humectant that serves as a carrier agent. Flavoring ingredients in e-liquids are often identified vaguely as “natural or artificial flavors,” without labeling of specific substances. The safety of flavorings in e-liquids has been evaluated by the FDA primarily for oral intake; at the level of intended use, they are generally recognized as safe (GRAS). The primary humectants (along with water) in e-liquids are propylene glycol and glycerol. Both are also GRAS based on their use in dermal products and as a vehicle for drugs. Ethylene glycol, a solvent used as antifreeze, has been identified in some e-liquid samples even when not listed on the ingredient label, although this is not common.

Unlike combustible cigarettes, which come in either plain tobacco or menthol, the range of flavors in e-cigarettes is vast. Across brands, there are over 7000 unique e-liquid flavors. JUUL pods, for example, come in tobacco, menthol, mint, cucumber, cream, mango, and fruit flavors.

According to the FDA, such kid-appealing flavors are a big reason for the current epidemic of vaping among teens and young adults, and their introduction was a deliberate and irresponsible attempt by manufacturers to entice underage customers. The numbers seem to bear this out—95% of college students and 71% of young adults choose fruit or candy-like flavors for their first e-cigarette use. In contrast, only 44% of adults age 30 or older chose flavored e-liquids for their first e-cigarette.

In November 2018, the FDA initiated plans to ban the sale of flavored e-liquids—except for tobacco, menthol, and mint flavors (those deemed to be less attractive to minors)—from all non–age restricted in-person retail entities such as convenience stores (vape shops are age-restricted). At the same time, the FDA announced plans to ban menthol and all other flavorings from combustible cigarettes.

What are the potential harms of e-cigarettes?

One fact is clear: e-cigarettes contain fewer (and lower levels of) toxic and cancer-causing substances than do combustible cigarettes. A heavy smoker is likely to have better health outcomes after switching to e-cigarettes as a means of tobacco cessation. But can the same be said for a nonsmoker who becomes a vaper?
In general, evidence is accumulating that vaping is not harmless. Harms may result from the device itself, known constituents of e-liquids, or from byproducts of aerosolization. Of most concern is potential long-term cardiovascular, respiratory, and cancer-causing effects; effects on the developing brain of adolescents; and effects on pregnant women. Secondhand bystander exposure is also a concern.

**Injury from device malfunction**

The e-cigarette itself has been known to spontaneously ignite or explode due to overheated lithium-ion rechargeable batteries. This has resulted in an estimated 2035 injuries presenting to US emergency rooms between 2015 and 2017. These injuries included lacerations, third-degree burns, loss of body parts (including eye, tongue, and teeth), and death.\(^{12}\)

**Nicotine dependence and addiction**

Terminology for nicotine dependence and addiction has recently changed. *DSM-5* defines “tobacco use disorder” as the overarching terminology encompassing the physical and/or psychological impact of a person’s tobacco use.\(^{13}\) The American Psychiatric Association developed this terminology to cover these effects of combustible tobacco products, but the concepts are useful in discussing the physical and psychological aspects of nicotine use from e-cigarettes as well. However, much of literature concerning nicotine uses the term “dependence” to describe symptoms of compulsive use of tobacco products.\(^{6}\)

Evidence that e-cigarettes result in nicotine dependence is substantial.\(^{6}\) Nicotine stimulates the release of multiple neurotransmitters, primarily dopamine, which results in a pleasurable (and reinforcing) experience for the user. Dependence is characterized by withdrawal symptoms if nicotine is suddenly discontinued, including irritability, frustration, anxiety, difficulty concentrating, increased appetite and weight gain, insomnia, and nicotine craving.

E-cigarettes deliver nicotine in a pharmacokinetic profile similar to that of nicotine from combustible cigarettes, and plasma nicotine concentrations after typical, ad lib use of an e-cigarette are similar to those attained with smoking combustible cigarettes.\(^{6}\) The type of device and user vaping behavior can modify the delivery of nicotine to the user; higher-wattage third-generation modular devices and longer puff duration (but not higher puff velocity) deliver more nicotine.\(^{14}\) These factors suggest that the dependence potential of one brand of e-cigarette may vary from another. Users of these higher-powered e-cigarettes tend to use e-liquids with lower nicotine concentrations. Experienced vapers can fine-tune their vaping behavior to titrate their nicotine intake to match the level of their craving for it.

Research shows that the high addiction potential of tobacco products is related to both the physiologic effects of nicotine and the stimulus context that occurs during the act of nicotine administration—the pleasant ritual of lighting up a cigarette (or presumably, an e-cigarette) and the associated sights, smells, and hand-to-mouth movements. It is plausible that the desirable flavors added to e-liquids may contribute to this effect.\(^{6}\)

**Nicotine as a bridge to smoking combustible cigarettes**

E-cigarette use by teens and young adults is associated with an increased risk of future combustible cigarette use. This had long been suspected and was confirmed in a recent meta-analysis that found that people ages 14 to 30 who had ever used e-cigarettes were 3.6 times more likely to report combustible cigarette smoking at follow-up. This finding remained significant even when adjusted for demographic, psychosocial, and behavioral factors that might be expected to influence susceptibility to tobacco smoking.\(^{15}\)

This association was confirmed in a recent study limited to high-school students, where individuals using e-cigarettes in the past month were between 4 and 7 times more likely to be smoking combustible cigarettes at follow-up. Of interest, this relationship was unidirectional: current use of combustible cigarettes did not predict future use of e-cigarettes.\(^{16}\)
Nicotine's effect on the developing adolescent brain

Nicotinic acetylcholine receptors (nAChRs) regulate critical aspects of brain development in adolescence and early adulthood (through the mid-20s), so nicotine exposure during this period might be expected to have some clinical effect. Studies have confirmed that even short-term exposure to a low dose of nicotine can produce lasting change in the adolescent brain, with effects on addiction, cognition, and emotional regulation.

Chronic nicotine exposure can sensitize adolescents to cocaine and make them more susceptible to cocaine abuse. Adolescent (but not adult) nicotine exposure has been shown to result in reduced attention span and enhanced impulsivity in adulthood and to result in long-term emotional response alterations (eg, increased anxiety, depression).

Effects on pregnancy and the developing fetus

Nicotine easily crosses the placenta and is metabolized more slowly in the fetus (and in infants) than the mother. Cumulative exposure has uncertain fetal and neonatal consequences, but may result in more toxicity than when compared to teens and adults.

Based on known risks associated with smoking combustible cigarettes, potential areas of concern with e-cigarettes include an increased risk of placental abruption, stillbirth, and preterm birth. Decreased birth weight is a known complication of nicotine.

Evidence suggests that exposure to nicotine during pregnancy may have lasting deleterious consequences for brain development, including detrimental effects on cognition. There is also potential concern for increased risk of lower respiratory tract infections and asthma in infants and young children.

Unfortunately, there is very limited evidence of the effect of nicotine replacement therapy (eg, nicotine gum, nicotine patch) during pregnancy (which would be a closely analogous exposure to e-cigarettes), and none regarding e-cigarette use during pregnancy.
Cardiovascular disease
There is currently no available evidence regarding long-term effects of nicotine or other aerosol components from e-cigarettes on any clinical cardiovascular outcome (ie, coronary artery disease, stroke, and peripheral artery disease). However, acute endothelial dysfunction has been noted after nicotine exposure via inhaler and local infusion; this finding is of uncertain significance for later development of these outcomes, but merits further study.

Nicotine has well-known sympathomimetic effects, including transient heart rate and blood pressure increases, constriction of coronary arteries, and increased myocardial oxygen consumption. Overall, there is substantial evidence that heart rate increases shortly after using a nicotine-containing e-cigarette, moderate evidence of diastolic blood pressure increases, and limited evidence of short-term increases in systolic blood pressure. However, there is currently insufficient evidence of long-term changes in heart rate, blood pressure, or cardiac architecture and function.6

Respiratory disease
Few e-liquid constituents have been studied specifically for safety when aerosolized and inhaled, but some have established adverse effects on respiratory health. Examples of these are diacetyl, acetylpropionyl, and acetoin; 90% of tested e-cigarettes contained one or more of these substances. Another study found that a majority of sweet-flavored e-liquids contained diacetyl and/or acetylpropionyl.6

Diacetyl and acetylpropionyl are used as a butter flavoring in microwave popcorn. Studies of workers in microwave popcorn manufacturing facilities demonstrated an increased incidence of respiratory disease, including chronic bronchitis, asthma, and bronchiolitis obliterans. Animal studies have demonstrated pulmonary fibrosis after exposure to acetylpropionyl. Bronchiolitis obliterans has also been identified in workers involved in flavoring manufacturing.20 Further studies are needed to determine if these substances pose long-term respiratory risks to vapers.

The humectants propylene glycol, glycerol, and ethylene glycol can irritate the upper respiratory tract, and their water-absorbing properties are thought to be responsible for complaints of dry throat associated with vaping. There have been no studies of potential long-term health effects when these ingredients are inhaled.6

Exposure to known toxicants, carcinogens, and heavy metals
In general, any compound that can cause DNA damage by production of reactive oxygen species or other intermediates, can act as a carcinogen, as can those compounds that interfere with DNA repair. There is substantial evidence that components of e-cigarette aerosols can promote production of reactive oxygen species and cause oxidative stress.

Many volatile and semi-volatile organic compounds have been identified in e-cigarette solutions, with additional compounds, including formaldehyde and acetaldehyde, being generated by the heating and aerosolization process. Formaldehyde is the most important carcinogen noted in e-cigarette aerosols, as it has been detected at concentrations that exceed usual exposure limits, with potential risk for nasopharyngeal and lung cancers.6

Significant levels of chemical toxicants have been found in the urine of adolescent vapers. The use of sweet, fruit-flavored e-liquids has been found to result in higher levels of toxic (and carcinogenic) chemicals in urine samples than have other e-liquid flavors.21 An increasing number of studies has also found toxic metals such as lead, nickel, and chromium in e-liquid emissions.2 This is a relevant finding because of the known serious health effects of exposure to metals, which include neurotoxicity (lead), cardiovascular disease (lead), and lung cancer (nickel and chromium). Most studies have been done on first-generation e-cigarettes, where it is speculated that the metal coils could be leaking to the aerosol. The relevance to third-generation devices, where this may be less likely to happen, is uncertain.
Fed-up with the rising number of school-age children purchasing e-cigarettes over-the-counter, in the summer of 2018, Scott Gottlieb, the FDA commissioner, ordered a large-scale undercover sting of brick and mortar stores selling these items. This netted 1300 instances of illegal sales to minors, resulting in warning letters to some stores and and monetary penalties to others. Sales of e-cigarettes to minors may be part of a larger scale problem with tobacco products in general; in February 2019, the FDA initiated a “No-Tobacco-Sale-Order” (NTSO) complaint against some retail locations of both Walgreens and Circle K Stores for repeated sales of tobacco products, including combustible cigarettes and cigars, to minors. If the NTSO complaint is successful, these retail outlets will be forced to suspend all tobacco product sales for 30 days.

Buying from an internet storefront has, until recently, been an easy option for kids who have access to a credit or debit card. The FDA has recently tightened up on this avenue of purchase by requiring heightened online identity and age verification from online retailers. E-cigarette manufacturers have been asked to cooperate in removing sales listings of their products from eBay and other resellers, where age verification is not likely to happen, but many such listings are still available.

Unfortunately, social media offers underage teens a convenient way to obtain e-cigarettes. With a smartphone and access to Snapchat or Instagram, it is easy to find older teens of legal age who purchase these devices in bulk and then sell them to younger kids for profit, using these platforms to advertise the time and place to meet for the transaction.

What are the potential benefits of e-cigarettes?
Adolescents use e-cigarettes for a variety of reasons, but smoking cessation is rarely cited as the primary reason. Instead, when surveyed in 2015 and 2016, high-school seniors cited experimenting (about 29%) or for the taste and entertainment as the primary reasons for

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**Secondhand aerosol exposure**

Bystander exposure to secondhand e-cigarette aerosol (including particulates and nicotine) occurs from the user’s exhaled breath and does not come from a side stream of the e-cigarette itself. Most studies have shown that there is some indoor pollution of air, above background level, in indoor environments when vaping occurs.

With a single vaper, these levels are lower than would be found with a combustible cigarette; however, when multiple vapers are present in a closed space, these levels rise rapidly. Studies performed at vaping conventions showed extremely high levels of nicotine and particulates, comparable to that found in nightclubs. Indoor air pollution appears to be higher than the standard recommended by the Surgeon General, and it is possible that these levels may be of particular risk to pregnant women, children, those with lung disease, and especially those who work in vape shops or at vaping conventions.6

How do kids obtain e-cigarettes?
Teens seem to have little difficulty purchasing e-cigarettes, judging from the increasing number of users, although the FDA intends to change that.

The list price of a JUUL device is $34.99; a starter pack, including the device and 4 flavored pods of e-liquid, sells for $49.99.22 A variety of venues, including gas stations, convenience stores, and vape shops sell them, although proof of age is required. (A quick “where to purchase” search located 6 shops within walking distance of my suburban neighborhood).

Since 2016, when e-cigarettes came under the authority of the FDA, they have been regulated just like other tobacco products, including combustible cigarettes, cigars, and smokeless tobacco. The minimum age for legal sale of e-cigarettes and e-liquids is 18, although it is higher (19 or 21) in a few states; a lobbying effort is underway to raise the age to 21 nationwide.23 The FDA mandates that the purchaser of e-cigarettes must be checked for ID if he or she appears to be younger than age 27, with penalties to the merchant for violating this requirement.
vaping. Only 7% used e-cigarettes as a tool to replace smoking combustible cigarettes. This contrasts with older adults, who have increasingly turned to vaping as a smoking cessation tool. Most adult users are current or former smokers, while only 16% of adult e-cigarette users report having never smoked combustible cigarettes.

Evidence for e-cigarettes as an effective smoking cessation tool for adults is still limited. In 2015, based on data available at the time, the US Preventive Services Task Force considered the evidence insufficient to recommend e-cigarettes as a tobacco cessation tool, instead recommending behavioral interventions, alone or in combination with FDA-approved smoking cessation tools, for nonpregnant adults. This recommendation is in the process of being updated in 2019.

Several systematic reviews and meta-analyses of the literature have been published in the past 5 years, but these have been heavily weighted to observational studies since only 3 randomized controlled trials, ranging from 50 to 657 participants, had been reported prior to 2018.

Two early meta-analyses were generally positive. They suggested that nicotine-containing e-cigarettes were superior to non-nicotine e-cigarettes for smoking cessation at 6 months. Another concluded that 20% of individuals using nicotine-containing e-cigarettes would successfully quit smoking. However, a 2016 systematic review found that, in real life and clinical settings, e-cigarette use is associated with 28% lower smoking cessation.

The most recent systematic review based on the 3 randomized controlled trials mentioned above and 9 prospective cohort studies confirmed the superiority of nicotine-containing e-cigarettes in comparison with non-nicotine e-cigarettes. The included cohort studies suggesting a possible reduction in quit rates with use of e-cigarettes compared with no use of e-cigarettes. All evidence was considered of low or very low certainty.

In January 2019, an additional randomized controlled trial (886 participants, conducted through the UK National Health Service) compared second-generation e-cigarettes plus face-to-face behavioral counseling to the comparator condition, nicotine-replacement product of the participant’s choice, plus face-to-face behavioral counseling. In this trial, the e-cigarette group had a 1-year abstinent rate nearly twice that of the nicotine-replacement group (18% versus 9.9%).

While these findings will need to be confirmed with additional studies, they suggest that e-cigarettes may have a valuable role in smoking cessation for adults. Whether the study's results can be replicated outside of the UK National Health Service remains to be seen.

Balancing the public health consequences of e-cigarettes: the FDA’s dilemma.

The FDA is growing increasingly frustrated over the epidemic of teen vaping. In an announcement informing the public of recent precipitous increases in teen vaping, Commissioner Gottlieb included a carefully worded threat to the e-cigarette industry that if such trends continue, the FDA could be “forced to consider regulatory steps that could constrain or foreclose” the availability of e-cigarettes, even for adults. This tops off 2 years of increasing scrutiny and increased regulation of the e-cigarette industry, with JUUL a repeated target.

An important factor in such regulation is the fact that most e-cigarette manufacturers have not yet had to officially meet the FDA’s public health standard, which states that any tobacco product introduced to the US market since 2007 must show a net public health benefit. Achieving this standard would require that e-cigarettes meet the following criteria:

A. Be less risky to the user than combustible tobacco cigarettes
B. Not cause more people to start smoking combustible cigarettes; and
C. Not cause fewer people to quit smoking combustible cigarettes.
Most e-cigarettes (those already on the market when they fell under FDA jurisdiction in 2016) have not yet been scrutinized for this standard, as the FDA has allowed these manufacturers until 2022 to submit applications for “pre-market” review and authorization while remaining on the market.6, 35

While there are definite biological effects (primarily, dependence on the device/nicotine), a panel convened by the National Academies of Sciences, Engineering, and Medicine concluded that there is not enough information on long-term health effects of e-cigarettes. The panel concluded that “switching from smoking combustible cigarettes to use of e-cigarettes only will conclusively reduce exposure to many toxicants and carcinogens and will presumably result in better long-term (and possibly short-term) outcomes,” apparently satisfying criterion A based on current evidence.6

With regard to criteria B and C, evidence suggests what while e-cigarettes may increase the risk of teens and young adults unidirectionally transitioning to smoking combustible cigarettes (or using them along with e-cigarettes), there is also likely some benefit to adult users who want to quit smoking combustible cigarettes.6

At present, the rapidly increasing use of e-cigarettes is outpacing the accumulation of evidence regarding its harms versus its benefits. These may be largely generational: the harms of addicting an entirely new generation to nicotine versus the immediate and long-term morbidity and mortality benefits to an older generation who may already be suffering the consequences of its own addiction. The FDA has the herculean task of sorting this out while protecting everyone.

For more information, see the Tobacco Use Disorder Clinical Overview in ClinicalKey.

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References


