E-Cigarettes: The Science Behind the Smoke and Mirrors

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E-cigarettes are a diverse set of devices that are designed for pulmonary delivery of nicotine through an aerosol, usually consisting of propylene glycol, nicotine, and flavorings. The devices heat the nicotine solution using a battery-powered circuit and deliver the resulting vapor into the proximal airways and lung. Although the current devices on the market appear to be safer than smoking combusted tobacco, they have their own inherent risks, which remain poorly characterized due to widespread product variability. Despite rising use throughout the United States, predominantly by smokers, limited evidence exists for their efficacy in smoking cessation. Pending regulation by the FDA will enforce limited disclosures on the industry but will not directly impact safety or efficacy. Meanwhile, respiratory health practitioners will need to tailor their discussions with patients, taking into account the broad range of existing effective smoking cessation techniques, including pharmaceutical nicotine replacement therapy. *Key words: e-cigarettes; cigarettes; smoking cessation; nicotine replacement; regulation; safety; harm reduction.* [Respir Care 2016;61(8):1122–1128. © 2016 Daedalus Enterprises]

Introduction

The term "e-cigarette" is used to refer to an array of devices marketed in the United States and internationally that vaporize a nicotine-containing solution for inhalation. The first e-cigarette is thought to have been invented in Hong Kong in the early 2000s and reached the United States shortly thereafter in small numbers. In recent years, however, their use and popularity have exploded. By 2014 there were >450 different brands of e-cigarettes,[1] 6 tobacco companies had acquired or developed their own device,[2] and 12.6% of United States adults[3] along with 13.4% of high school students[4] had tried an e-cigarette. However, concurrent with this rapid rise in use have been increasing questions about their safety, efficacy, and potential impact on public health.

Beginning in August 2016, e-cigarettes will be subject to recently announced regulations by the FDA, although the rules are currently subject to legal challenge from the e-cigarette industry. While they are often assumed to contain pharmaceutical or food-grade chemicals, no rules, current or pending, require that devices labeled "e-cigarettes"

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do contain pharmaceutical or food-grade chemicals, and no regulations directly address their safety or efficacy. This may be in part because both the academic and public health communities are split on their perceived safety and potential impact. A recent review by Public Health England asserted that e-cigarettes are "95% less harmful [to one's] health than normal cigarettes,"[5] based on the absence of constituent chemicals found in combusted tobacco, whereas the American Lung Association[6] has recommended against their use for cessation, and other organizations have called for further study[7] or more aggressive regulation.[8]

Although many people report using e-cigarettes for smoking cessation, their efficacy has not been demonstrated in randomized clinical trials.[9,10] Despite this, the devices are notably similar to pharmaceutical nicotine replacement therapy products, such as gums, lozenges, patches, nasal sprays, and inhalers,[11] and may ultimately prove to be part of the same class. Meanwhile, researchers and public professionals have raised an array of concerns about their introduction into the market, including "renormalization" of smoking behavior, serving as a gateway to smoking for youth,[12] and delaying cessation in people who might otherwise quit.[13]

For the most part, e-cigarettes do not contain the chemicals in combusted tobacco smoke that have been tied to cancer and respiratory disease. On the other hand, little is known about the impact of the chemicals that are present in nicotine solutions and their impact after heating, aerosolization, and inhalation into the respiratory system. Despite the limited knowledge base and the concerns that have been raised, e-cigarettes continue to proliferate and may ultimately play a significant role in transitioning smokers away from combusted tobacco. Here we aim to review what is known about e-cigarette design and their impact on respiratory and cardiac health, along with a discussion of the limited evidence on safety and efficacy, in an effort to provide context for the inevitable questions and concerns from patients and colleagues.

Review of the Literature

Device Construction and Functioning

The earliest and most common models of e-cigarettes were designed as look-alikes for traditional combusted cigarettes. In general, these basic models have a cylindrical body with a mouthpiece at one end and an LED light at the other designed to mimic a lit cigarette.[14] General construction consists of the body, a cartridge containing nicotine solution, a heating element, and a battery. These models may be referred to in terms such as "cigalikes," whereas later models diverge significantly, adapting larger batteries and reservoirs (or "tanks") for nicotine solution in lieu of the cartridge[2] and frequently abandoning the LED or other efforts to appear similar to a cigarette or cigar.

On inhalation, a pressure- or flow-sensitive switch closes and connects the battery to both the LED and the heating element. The nicotine solution is brought into contact with the heating element through a wicking mechanism, from either the tank or the cartridge. The heating element vaporizes the liquid, and the aerosol is then drawn through the mouthpiece into the lungs. Tank models often replace the pressure switch in earlier models with a manual one, allowing the user to begin the vaporization process before inhalation. This eliminates the initial lack of vapor draw present with a flow switch.

Although a great deal has been published in the academic literature about device construction, solution constituents, and aerosol contents, the lack of regulation enforcing consistency limits our ability to make generalizations about e-cigarettes. In other words, the next generation of devices could differ substantially from the current ones, ranging from the appearance of the devices to their mechanism of vaporization to their choice of solution chemicals and even the amount of nicotine delivered.

Nicotine Solutions. Whereas most manufacturers use propylene glycol as a base solution (or "humectant"), others have used glycerol (ie, glycerin or glycerine) or other chemicals. Propylene glycol is generally accepted as safe in cosmetics and foodstuffs but has not been extensively studied as an inhalant or for long-term use.[15] Solutions are sold both in prefilled cartridges and as stand-alone preparations designed to fill tanks or refill used cartridges. These solutions can be purchased directly from e-cigarette manufacturers, online from independent vendors, or at local "vape shops" that may mix their own solutions.

Analysis of commercially sold liquids has demonstrated variable results in the United States market, with earlier testing having more common findings of contamination and lower grade materials. Recent testing of the solutions from 2 major vendors showed few impurities and a profile consistent with the use of pharmaceutical grade nicotine.[16] On the other hand, the first published analysis of an e-cigarette solution demonstrated contamination with diethylene glycol in a single sample.[17] This finding spurred early concerns about supply chain control[18] because diethylene glycol has been a lethal and toxic contaminant in multiple mass poisonings in emerging markets.[19] Many devices and their refill solutions are imported from China; analysis of solutions on the Chinese market found primarily propylene glycol, glycerol, and tobacco-specific impurities in addition to nicotine and flavorings consistent with United States findings.[20]

Importantly, nicotine content in e-cigarette solutions has also been variable, often not matching labeling.[21] Some

vendors sell highly concentrated solutions, either designed for direct use or dilution with propylene glycol by the purchasers. These solutions have raised concerns for potential poisonings,[22] especially given the rise in number of calls to poison centers since the introduction of e-cigarettes.[23]

Particulate Matter and Effects on the Respiratory System. Current understanding of e-cigarette impact on human physiology is derived primarily from analysis of nicotine solutions and the emitted vapor and secondarily from a small number of studies of nicotine delivery and its associated physiologic response. For the most part, studies have used devices with propylene glycol-based solutions. To date, there are no studies of the impact of e-cigarettes on long-term respiratory health.

Of particular concern has been the heating process to vaporize the solution. Little is known about the long-term inhalation of propylene glycol in vapor form.[15] When propylene glycol or glycerol is directly heated, toxic aldehydes such as formalin (a significant known carcinogen),[24] acetaldehyde, and acrolein are naturally formed in a secondary reaction.[25] Increased heating element temperature coupled with inadequate solution delivery to the heating element has been associated with higher levels of aldehydes[24] in device testing. In addition to known toxins, many organic compounds within the aerosol are unidentifiable.[26] These compounds, complexed into particles that compose the aerosol, are of a size distribution closely mirroring cigarette smoke[27] and theoretically can reach the distal bronchioles and alveoli.[28]

Cell culture models have demonstrated a cytotoxic effect of certain e-cigarette aerosols. For example, one experiment demonstrated necrotic cell death in addition to lower macrophage and neutrophil function in an in vitro model of 2 separate human epithelial cell lines.[29] Additionally, once infected with bacteria, those cells exposed harbored the organisms at a higher concentration. Other studies have only uncovered cytotoxicity using particular brands or flavors[30] or cell types.[31] Finally, one study demonstrated no cytotoxicity but did show increased concentration of an inflammatory mediator (interleukin-6) in cells exposed to e-cigarette solution.[32]

There is limited information about the impact of e-cigarettes on respiratory mechanics. One study of cigarette smokers without lung disease who used e-cigarettes ad lib for 5 min found that device use worsened airway impedance, lung resistance, and peripheral pulmonary resistance measured with special equipment.[33] Despite these changes, spirometry was unchanged in the study, making interpretation of the short-term findings difficult. Other investigators have specifically noted that FEV_1/FVC changes with exposure to combusted cigarette smoke but not e-cigarette vapor.[34]

Secondhand smoke is a real and substantial risk with the use of combusted cigarettes, whereas its risk with e-cigarettes is unclear, if present. E-cigarettes generally produce vapor only on inhalation, and the exhaled vapor contains levels of nicotine and volatile organic compounds markedly lower than those in true tobacco smoke.[35]

Nicotine Delivery, Deposition, and Uptake. The cardiovascular impact of combusted tobacco smoke has a complex set of considerations related primarily to carbon monoxide and other combustion products. Thrombosis, platelet activation, and inflammation contribute to reduced myocardial blood supply, which is compounded by reduced oxygen delivery from carbon monoxide. Nicotine increases heart rate and blood pressure, driving up myocardial demand, synergistically increasing the risk of cardiac ischemia in the setting of tobacco smoke.[36] Critically, however, nicotine is considered to be safe when delivered alone as pharmaceutical nicotine replacement therapy.[11]

As expected, heart rate increases with exposure to e-cigarette vapor as plasma nicotine levels rise.[37,38] For smokers trying e-cigarettes for the first time, plasma nicotine levels generally track with increasing solution nicotine concentrations.[39] However, more experienced users appear to learn how to inhale differently, with longer "puffs"[40] and can generate higher plasma nicotine levels.[41]

Early studies using primarily first generation e-cigarettes showed that they delivered low or even negligible plasma levels of nicotine.[38,42] Later studies, particularly in experienced users, have shown nicotine plasma concentrations similar to those of combusted tobacco cigarettes.[41,43] The rapid evolution in nicotine delivery is probably multifactorial, related not only to optimized solutions and devices capable of delivering higher concentrations of nicotine in the vapor, but also to increasing aerosol deposition into the lungs and distal alveoli while bypassing the oral airway. Nevertheless, although e-cigarette aerosol has a particle size distribution similar to that of combusted tobacco smoke,[28] serum testing has indicated a slower uptake of nicotine into plasma.[43] This probably indicates that the deposition still remains predominantly in the oral mucosa and oral airways rather than the alveoli and that absorption is into the venous circulation rather than arterial.

Epidemiology

As of 2014, 12.6% of United States adults report having tried an e-cigarette, including 49% of daily cigarette smokers, of whom 16% report currently using e-cigarettes as well.[44] Use is more common in younger adults; 21.6% of people 18–24 y old have tried e-cigarettes versus 3.7% of people >65 y old.[3] Individuals who report recently quitting tobacco are significantly more likely to report active use of e-cigarettes, with 22% of recent quitters reporting

use versus 3.7% of all adults.[44] Overall, use of e-cigarettes by adults is primarily limited to smokers and recent former smokers, with only 0.4% of never smokers and 0.8% of smokers quitting >4 y prior reporting e-cigarette use.[44]

E-cigarette use appears to be increasing among in young adults. 13.4% of high school students tried an e-cigarette in 2014 (2 million students), up from 4.5% in 2013 and 1.5% in 2011. Concurrent with the increase in reported e-cigarette use has been a drop in the use of combusted cigarettes, whereas e-cigarette use exceeds combusted cigarette use across all ages.[4] The vast majority of adolescents who regularly use e-cigarettes are already using combusted cigarettes.[45] However, concern remains that e-cigarettes may serve as a low-risk and palatable gateway to combusted tobacco use,[46] ultimately increasing morbidity rather than decreasing it.

Efficacy

Decades of research on nicotine replacement therapy have demonstrated that multiple forms of delivery, including the patch, gum, lozenge, nasal spray, and inhaler, can be made both safe and effective.[11] Given history and the relative similarity between e-cigarettes and other forms of nicotine replacement therapy, there is little reason to believe that a nicotine inhaler using propylene glycol and refined nicotine cannot be constructed to be effective for smoking cessation. However, existing nicotine replacement therapy products were developed within formal pharmaceutical processes and marketed and sold under governmental regulation, whereas to date, randomized control trials of e-cigarettes from various manufacturers have failed to demonstrate efficacy. Of the 3 meta-analyses in press, 2 found a probable increase in cessation,[47,48] whereas a third,[49] taking into account more non-controlled and observational trials, found that they may *suppress* cessation, indicating that the current literature is insufficient to make firm conclusions in either direction.

Two randomized trials have directly addressed cessation. A New Zealand-based trial randomized participants to a first generation electronic cigarette with 16 mg of nicotine, a placebo device, or access to nicotine patches. Trial participants were provided with electronic cigarettes or given vouchers to obtain their own nicotine replacement. The trial found no significant effect for the nicotine e-cigarette (or for patch vouchers) over placebo. In the second trial, conducted in Italy, smokers not intending to quit were randomized to 3 conditions: a placebo device, a commercial e-cigarette model, or the same model followed by a taper. Although cessation rates were higher in the nicotine arms (13 and 9%) than for placebo (4%), the results were not statistically significant. The pooled results of these 2 trials indicate that nicotine-containing e-cigarettes outperform placebo e-cigarettes (RR 2.29).[47,48] Notably, both of these trials used early generations of e-cigarettes with a lower delivery of nicotine than current devices on the market.

In the only randomized controlled trial conducted in the United States, investigators randomized smokers interested in cutting back on smoking to either nicotine-containing e-cigarettes or placebo. At 3 weeks, participants receiving the nicotine e-cigarette were smoking slightly fewer combusted cigarettes, and the reduction was directly related to the number of nicotine-containing e-cigarettes used.[50]

Taken together in context, these trials are consistent with the theory that e-cigarettes can potentially be effective, but reinforce the limitation that there is no true class effect. In other words, the broad variability in functioning and nicotine delivery across manufacturers and device evolution precludes assumptions about any single device based on studies of competitors. Currently, no individual device has been demonstrated to be effective, and no class effect across devices should be assumed.

Safety, Harm Reduction, and Regulation

There is little real debate that the majority of devices on the market are less harmful than the use of combusted tobacco. Based on constituent analysis, e-cigarettes have been estimated to have a relative harm profile somewhere between nicotine replacement therapy (2% of cigarette smoke) and oral tobacco use (5% of cigarette smoke),[51] in other words ≥20-fold less dangerous than cigarette smoke. Given this, it seems more appropriate to compare safety expectations with pharmaceutical products that are also constructed with refined chemicals rather than processed tobacco.

To date, most short-term adverse effects have occurred due to poor manufacturing standards. Battery explosions,[52,53] solution contaminations,[54] and high levels of toxic by-products due to higher heating element temperatures have all been reported.[24,55] Although these problems have led to serious complications ranging from third degree burns and ICU admissions[53] to lipoid pneumonia,[56] they are also the most straightforward because they have been solved in other products (such as pharmaceuticals, cosmetics, pet foods, and children's toys) through regulation and supply chain management. Of greater concern are the unknown long-term consequences of inhalation of propylene glycol and flavorings, compounded with the risk that e-cigarettes may evolve in directions inconsistent with their currently known profile.

At the moment, the FDA has put forward a fairly minimalist set of regulations for e-cigarettes.[57] The regulations will subject e-cigarettes to the same level of scrutiny as tobacco products, including restricted marketing toward youth, warning labels, evidence-supported claims about modified risk, and disclosure of ingredients.[58] Rules to

prevent youth access go into effect in the summer of 2016 while other rules will be phased in over the next 2 years. Importantly, these proposed regulations would not enforce manufacturing standards, require supply chain management techniques, eliminate contaminants, cap heating element temperatures, or otherwise address many of the known short-term harms. What is currently unclear is how the FDA will enforce "premarket" review of newly developed e-cigarettes, an expensive and time-consuming process that could potentially favor larger manufacturers and existing legacy combusted cigarette producers with deeper pockets.

Rapid change in uptake profiles over the past several years indicates that the devices can be optimized, and there is no reason to believe that they have stopped evolving. In the long term, assuring safety for a product without tight definitions and regulatory oversight is difficult, particularly if the market consolidates around the existing multinational tobacco companies that need to protect existing combusted tobacco sales.

Summary

When this manuscript was written, a search for "e-cigarettes" on PubMed returned 1,795 papers, with nearly half of them published in the preceding 12 months. Despite the explosion of literature, we still can say little about any given device purchased in a convenience store: how well it might work to help a patient quit, whether its battery works properly, or whether its nicotine solution is uncontaminated. This is through no fault of the researchers but simply indicates that some of these questions may be impossible to answer concretely as long as what we call e-cigarettes remain such a broad and diverse class of products.

A common question to health-care practitioners is the simple "what should I do?" from patients, friends, and family alike. E-cigarettes are increasingly used by smokers for both cessation and harm reduction.[9,59] For those individuals who have successfully transitioned off of combusted tobacco, simple encouragement to wean off of e-cigarettes and nicotine as tolerated makes more sense than abrupt cessation or an attempted transition to another form of nicotine replacement. The damage from continued, chronic inhalation of tobacco smoke, particularly in the respiratory patient, is immense and ongoing. Any tool that avoids that, whether nicotine replacement therapy, e-cigarettes, or otherwise, should be evaluated in that critical context. More difficult is the individual looking either to quit in the future or even simply to minimize their use of combusted tobacco without quitting. For these individuals, it is perhaps most useful to think of e-cigarettes as members of the nicotine replacement class, along with the patch, gum, and inhaler. At one end of this continuum are the pharmaceutical products that are safe, reliable, and effective, whereas at the other end are e-cigarettes that tend to be cheaper, more widely available, and heavily marketed and have higher consumer acceptance. Until e-cigarettes are regulated and standardized with clear evidence of efficacy, pharmaceutical products remain the more conservative choice and, under the Affordable Care Act, are also required to be covered without co-pay by insurers.[60] How future regulation will impact e-cigarettes or whether manufacturers will choose to pursue optimization of their devices for cessation and clinical trials remains unknown. Regardless, the rapid ascent of e-cigarettes demonstrates the feasibility of substituting "clean" nicotine for toxic, combusted tobacco smoke at a population level and provides hope for future public health strategies.

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