Review Article

E-cigarettes/electronic nicotine delivery systems: a word of caution on health and new product development

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Abstract: This paper describes the introduction, development, and proliferation of new electronic nicotine delivery systems (ENDS). The use of non-combustible tobacco products is considered a means for improving public health and reducing the mortality attributed to cigarette smoking. The effects and use of ENDS are described, with studies to date indicating that, despite differences in toxicity, there is insufficient evidence that ENDS leads to smoking cessation. Finally, research questions are proposed to address key unanswered questions about the effects of such systems.

Keywords: Electronic nicotine delivery system (ENDS); health hazards; harm reduction; smoking cessation; product technology; marketing

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Introduction

"*It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts*." —Arthur Conan Doyle (1859–1930)

Cigarette smoking is the major preventable cause of morbidity and mortality in the US and many other countries. Use of tobacco in the world is undergoing a significant change since the arrival of so-called electronic cigarettes. The first documented patent for this type of device was issued in Pennsylvania on August 17, 1965. However, it took several years of additional propagation before the beginning of mass production was initiated in China in 2003.

More than 460 different e-cigarette brands are currently on the market with over 7,700 flavors (1,2).

Most e-cigarettes structurally contain four different components, including (3):

(I) Cartridge or reservoir, which holds a liquid solution (e-liquid or e-juice) containing varying amounts of nicotine, flavorings, and other chemicals;
(II) Heating element (atomizer);
(III) Power source (usually a battery) and
(IV) Mouthpiece that the person uses to inhale. It is thus more appropriate to address these products as electronic nicotine delivery systems (ENDS).

In many ENDS, users' puffing activates the battery-powered heating device, which vaporizes the liquid in the cartridge. The person then inhales the resulting aerosol or vapor (called vaping, a word now officially sanctioned by the Oxford Dictionaries).

Development and marketing

Rapid development of ENDS resulted in several generations of more and more sophisticated, even computer-controlled, devices. New products and companies, including T-vapor and Juul, follow established patterns of new product

development, including efforts to increase sales and reduce health hazards (4,5). T-vapor is comparatively a new category that uses real tobacco. T-vapor products are sold in two versions: heat-not-burn and infused. The market for t-vapor is projected to grow 60% during the next 10 to 15 years. The latest rapidly growing trend is a liquefied nicotine salts device delivery named Juul. This new type of ENDS delivers a rapidly absorbable concentration of dissolved nicotine, much higher than in a standard cigarette.

The unregulated markets facilitate this proliferation of multiple devices and delivery systems. In the same markets, standards for consumer protection and company production oversite are largely nonexistent. The global e-cigarette market is expected to reach about $27 billion by 2022.

The major means of distribution of ENDS are vape shops, supermarkets, online sales, tobacconists and vending machines. Among these channels, vape shops are estimated to generate the highest revenue for the e-cigarette market in 2018.

Product marketing is unfettered, but there is now a consensus that eliminating the use of combustible tobacco products would improve public health substantially, with a potential reduction of mortality and morbidity attributable to cigarette smoking (6). The vaping devices and their constituents are touted by their manufacturers as safer than smoking tobacco. But safer does not mean safe.

The legal status of e-cigarettes is currently pending in many countries. In the U.S., the FDA extended its regulatory power to include e-cigarettes on August 8, 2016. The FDA rule also bans access to minors. The latest FDA plan for tobacco and nicotine regulation, published in 2017, emphasizes the goal of nicotine reduction (3,7).

Globally, the regulation trend is still lagging. The Asian-Pacific region offers major growth opportunities for vendors. In that region, the large population growth with increasing rapid urbanization, contributes to the increase of level of education. People that are more educated have higher incomes and better access to information. The effect has been to markedly increase the demand for these products in this region. China has been the leader in the regional e-cigarette industry, with an estimated 40.3% share in 2017. After the U.S. and the U.K., China has been estimated to be the third largest e-cigarette market globally in 2017, which inevitably is expected to grow.

Competition in the e-cigarette industry is being restructured with major mergers and acquisitions among traditional major tobacco companies. British American Tobacco (now also owning Reynolds), Japan Tobacco Inc., Altria Group, and Imperial Brands have been the major players in this expansion.

In the attempt to increase market share, while promoting further addiction and dependence on nicotine, many of the companies use aggressive perfidious advertisement touting benefits of ENDS over medications proven to have some efficacy in smoking cessation like bupropion and varenicline.

According to a survey conducted by the Chinese Center for Disease Control and Prevention in 2014, 45% of students, aged 13–15 years old had heard of e-cigarettes and 1.2% had used them in the preceding 30 days. Further analysis suggested that for every 1% consumer shift from combustible cigarettes to their presumably less harmful counterpart, the market for e-cigarettes in the country increases by almost five billion dollars. Advertising campaigns have been educating consumers about the benefits of switching from combustible cigarettes to their presumably less harmful alternative, consequently driving the e-cigarette market in the country.

The phrase “presumably less harmful” overlooks the harm that results when use of e-cigarettes leads to use of regular cigarettes or promotes double use—both e-cigarettes and regular cigarettes. A US study showed that students who used e-cigarettes by the time they started ninth grade were more likely than others, to start smoking cigarettes and other combustible tobacco products within the next year (8). As a result, studies suggest that teens using e-cigarettes are at a greater risk for smoking cigarettes in the future, supporting the gateway theory where the driver is addiction to nicotine (9).

As with most addictive substances, nicotine increases levels of dopamine, a chemical messenger in the brain, which affects the parts of the brain that control motivation, reward and pleasure.

Types of ENDS devices

The initial first-generation products resemble traditional cigarettes. They are convenient to use, do not require cartridges or refill solutions and, in many circumstances, are the introductory product for many users. Rapid developments led to rechargeable e-cigarettes, which contained replacement or rechargeable nicotine cartridges and required batteries with chargers. These models and the subsequent ones have increased refilling tank capacity, which lasts longer due to rechargeable batteries.

Progressively, the user can adjust the length of puffs and output of the batteries, thus increasing the temperature of the heating element and the concentration of the vapor. These engineering features affect the chemical composition and potential toxicity of the ENDS aerosol (10). Independently, multiple color combinations, artistic designs, carrying cases, and accessories for ENDS support a variety of individual styles. Newer types (for example, Juul) are more technologically driven and include designs inspired by electronic pen drives, which appeal more to the generation of younger users.

At least four factors affect the amount of nicotine from ENDS that is absorbed into the bloodstream and reaches the nicotinic receptors in the brain:

(I) The nicotine concentration content in the product;
(II) How effectively the vaporization process transfers nicotine from the reservoir into the aerosol;
(III) Additives that may facilitate nicotine absorption;
(IV) Use habits (such as frequency and depth of inhalation) that can affect the bioavailability.

Various studies suggest large differences in nicotine vaporization between brands and within each brand. These differences are likely to be a function of not only nicotine concentration but also different types of heaters which react differently to the spacing and frequency of puffs employed in the studies.

To date, no study has carefully investigated the effect of different nicotine doses of ENDS to determine the effect of users' preferences. Furthermore, new generations of ENDS are likely to improve further nicotine delivery. Studies with these newer products are warranted.

ENDS effects

Propylene glycol and vegetable glycerin are the two major solvents creating vapors in ENDS. These solvents are also used extensively in many pharmaceuticals and skin products.

Studies of these nicotine solvents in the ENDS showed a variable degree of release of small amounts of potential carcinogens—including formaldehyde, acetaldehyde and acetone—depending on battery output voltage (10).

In a more recent study, while endothelial microvascular function and oxidative stress remained unaffected, acute vaping of an aerosol of propylene glycol/glycerol at high wattage and in large amount induced sustained tissue hypoxia, an airway epithelial injury and small airway constriction (11,12).

It is now widely accepted that the levels of emission of various potential toxic or carcinogenic substances during vaping are significantly lower than from combustion of regular cigarettes. Several studies suggest that although e-cigarettes are not without risk, they possibly produce fewer respiratory health issues compared to tobacco cigarettes. However, our knowledge gap in overall harm reduction and health benefits remains wide, and this cannot be translated as an assurance of absolute safety (13).

The major criticism of studies related to ENDS is based on the fact that they are performed mostly on animals and on cell or tissue cultures (incidentally, no studies provide information on the effects on the pulmonary interstitium, which may affect transitional remodeling of tissue as well as initiate or propagate various immunologic responses). They do not necessarily reflect pragmatic human use. The other human studies examining harm reduction are methodologically weak. This is because those studies are non-randomized, prospective studies, small and not scientifically validated, biased, and produce conflicting results. These other human studies are not evidence based or very clinically relevant.

Use of ENDS among youth and adults

There has been a continuous increase of use of ENDS among middle and high school students. According to a study from 2013, the "ever use" (tried at least once) increased from 3.3% to 6.8% (14,15). In another study: Tobacco Use Among Middle and High School Students—United States, between 2011–2016, an estimated 3.9 million U.S. middle and high school students used any tobacco product, with 1.8 million reporting current use of ≥2 tobacco products. Among youths, symptoms of nicotine dependence have increased in multiple tobacco product–users compared with single tobacco product users (10,14-16).

With adults, the primary issue is the degree to which ENDS use by current smokers represents harm reduction (by encouraging smoking cessation or smoking reduction) versus harm escalation by promoting greater nicotine intake through dual use and or continuation of tobacco use.

Earlier data from 2011 already showed that in the U.S., among adults who had tried e-cigarettes, a majority were also concomitant tobacco smokers—close to 10 million, while 3.8 million were former smokers and slightly below 2 million were never previous smokers.

It is obviously difficult to discuss overall ENDS safety, when considering a market that includes over 460 brands,

7,700 available flavors, thousands of liquid alternatives, considerable variability in product design and performance, and a lack of any standardization. Although these devices may deliver fewer toxic compounds compared with combustible cigarettes, the extent of which reducing exposure to these compounds will lead to meaningful reduction of adverse health effects remains unknown. Prior studies show that reducing the number of cigarettes smoked by greater than 50% does not necessarily lead to health benefits. The only documented benefit comes from a total, prolonged cessation.

Estimates report that the prevalence of e-cigarettes is doubling annually. Current tobacco smokers constitute the vast majority of the e-cigarette users. Among lifetime never-smokers, the prevalence of use of e-cigarettes is only 1%. As a result, it is currently impossible to draw firm conclusions about the health risks of ENDS as a whole.

Potential for smoking cessation?

To date, only a handful of studies have explored the efficacy of using ENDS for smoking cessation.

The majority of these studies consist of observational and web-based surveys, which by definition include many methodological caveats. These studies provide no evidence-based support for or against the possibility that e-cigarettes result in tobacco smoking cessation. Recently, a methodologically improved, pragmatic controlled trial of motivation for smoking cessation using e-cigarettes, in two arms of the study, showed that use of e-cigarettes was not as efficacious as hypothesized (17).

At least 25% to 35% of current tobacco smokers have tried ENDS, with their proportion increasing rapidly. Meanwhile however, e-cigarettes studies have shown that only 1% to 15% of those who continue to smoke were able to reduce the usual brand-smoking intake by around 90%.

In another recent study of smoking cessation attempts among hospitalized patients six months after their hospital discharge, patients who reported any use of e-cigarettes were less likely to have quit smoking regular cigarettes than those who did not use e-cigarettes. On the other hand, patients who received free quitting support treatment reported less use of e-cigarettes but were less likely to have quit at six months if they used e-cigarettes than if they did not use them (18).

At the present time there is insufficient data to suggest that using ENDS and other nicotine replacement therapies results in quitting or reducing tobacco smoking.

Role of ENDS in cancer patients

As in any other condition, it is well accepted that smoking cessation is recommended for patients with neoplastic diseases and, in particular, lung cancer. A study conducted in a comprehensive cancer center with a well-established tobacco treatment program showed that e-cigarette users were as likely to be smoking at the time of follow-up as nonusers were. That study also showed that, when using an intention-to-treat analysis, e-cigarette users were twice as likely to be smoking at the time of follow-up as nonusers were (19). The potential interactions of ENDS with cytotoxic cancer therapeutics are also unknown. In vitro evidence shows that nicotine stimulates proliferation, migration, invasion, and angiogenesis and decreases cancer cell death from irradiation and chemotherapy (20,21).

Human bronchial cells grown in a medium exposed to e-cigarette aerosol showed a similar pattern of gene expression to those grown in a medium exposed to tobacco smoke.

Policy statements from the American Association for Cancer Research and the American Society of Clinical Oncology indicate that there is insufficient evidence to recommend ENDS to cancer patients, and the potential benefits or harms of ENDS use by cancer patients are unknown (22).

Because of so many remaining unanswered questions, we make the following suggestions (certainly not exhaustive) that focus on potential further important research project needs:

- How do different design features relate to abuse and toxicity, and what is the abuse potential of different types of ENDS?
- How are various compounds in ENDS affected by heating, changes in chemical composition, or pH influencing their absorption into the bloodstream?
- How are e-liquid additives affecting the bioavailability of these compounds?
- Can ENDS be used effectively in combination with existing FDA-approved smoking cessation medications?
- How do ENDS affect smoking reduction and cessation outcomes?
- Does transition from smoking to ENDS confer a long-term health benefit?

As far as e-cigarettes and all ENDS are concerned, Arthur Conan Doyle's word of caution is warranted:

"*It is a capital mistake to theorize before one has data. Insensibly one begins to twist facts to suit theories, instead of theories to suit facts.*"

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Footnote

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