Health Risks Associated with e-Cigarettes, Vaping, and JUUL

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Key Points

- The advent and rapid product development of e-cigarettes has created new challenges and opportunities in the area of tobacco control.
- Scientific knowledge is lagging behind the rapid uptake of ENDS and not much is known about short- or long-term health risks.
- There is substantial evidence that e-cigarette use increases risk of ever using combustible tobacco cigarettes among youth and young adults.
- There is not enough evidence to support the claim that ENDS can help people quit smoking.
- Suggested policies and actions to protect public health include discouraging ENDS use among youth, increasing ENDS safety, and determining with more precision whether and under which conditions ENDS could serve as an effective smoking aid.

Introduction

In the last decade, the advent and rapid product development of e-cigarettes brought new challenges and opportunities in the area of tobacco control. As these products are promoted as both the solution for the tobacco epidemic by some and as the beginning of a new epidemic by others, policies to respond to them continue to rapidly evolve.

"E-cigarettes" is a generic name for a heterogeneous group of products that may or may not contain nicotine [1]. The focus of this report is on ENDS (Electronic Nicotine Delivery Devices), or e-cigarettes that deliver nicotine combined with other chemicals (referred as "e-juice" or "e-liquid").

This brief describes the ENDS product landscape, their known short- and long-term health effect, ENDS use and associated risks among youth, and ENDS as a harm reduction and/or cessation tool to quit combustible tobacco cigarettes, referred as "cigarettes" in this report.

The ENDS Landscape

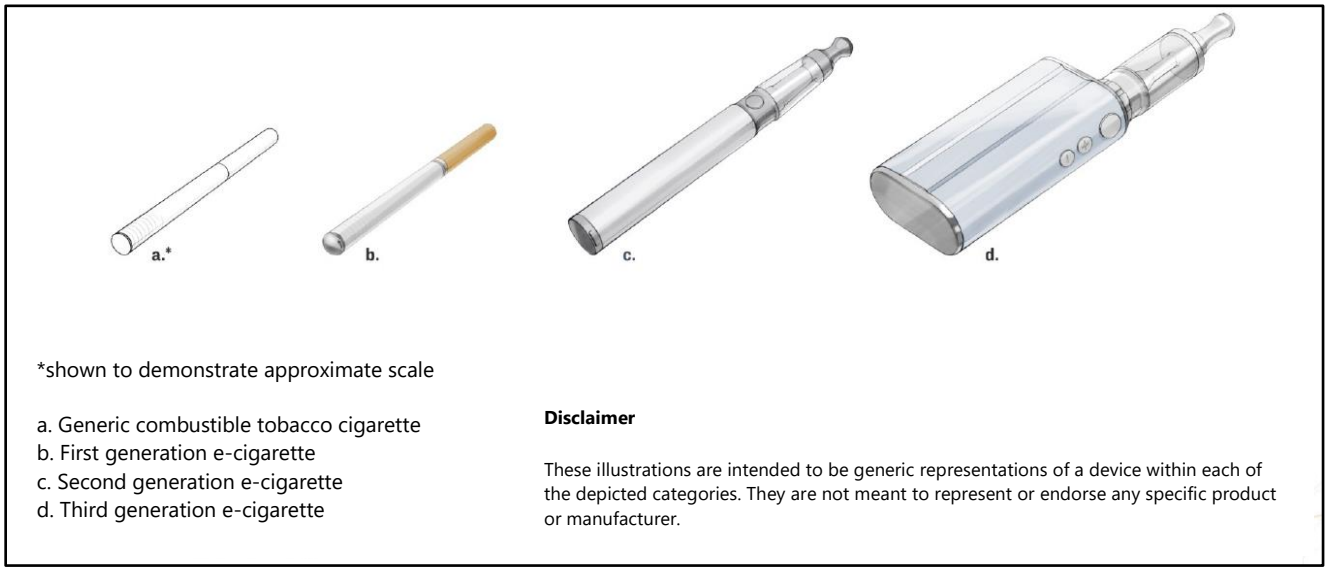
Currently there are four generations of ENDS, all still available on the market. ENDS vary in price, aesthetics, and technology. Each generation seems to cater to different consumers, ranging from occasional users interested in practical, on-the-go options, to regular users who prefer to manually refill ENDS and are very specific in their e-liquid preferences.

The *first generation* of e-cigarettes (Figure 1b) – also known as "cig-a-likes" – comes with a sealed e-liquid cartridge and a rechargeable device, which heats a coil and turns the liquid into vapor. "Cig-a-likes" can be a one-time product, disposable after the cartridge is empty, or refillable with the purchase of a new sealed cartridge. They are referred to by the e-cigarette industry as "closed systems," meaning they are not made to be disassembled for refilling.

The *second generation* of ENDS are "open systems," refilled manually by unscrewing the component parts and squeezing e-liquid from a bottle into an area usually referred to as an "atomizer" or "cartomizer," depending on the brand (Figure 1c and Figure 2). They are often referred as "vape pens."

The *third generation* has been referred as MODS (for "modified"), or advanced personal vaporizers (APVs), also refillable by manually squeezing e-liquid from a bottle. MODS are larger than e-cigarettes and vape-pens (Figure 1d) and have a more sophisticated temperature control. According to manufacturers, MODS do not contain any circuity or electronic components, but instead a mechanical "fire button" that, when pressed, makes a connection between the battery and the atomizer coil, causing it to heat up.

Figure 1: Generations of ENDS products



What do these devices deliver?

The first 3 generations of ENDS deliver "e-liquids" in cartridges or small bottles. The main constituents of e-liquids are flavors and nicotine, dissolved in propylene glycol (PG) and/or vegetable glycerol (VG).[2] The amount of nicotine varies and is delivered as freebase (FB) nicotine, which is also used in commercially available cigarettes.[3] The exact content of e-juice used in ENDS is proprietary, as is the case with traditional combustible cigarettes.

Figure 2: Loading "e-liquid" into cartridge



The "disruptor": JUUL and other POD-based products

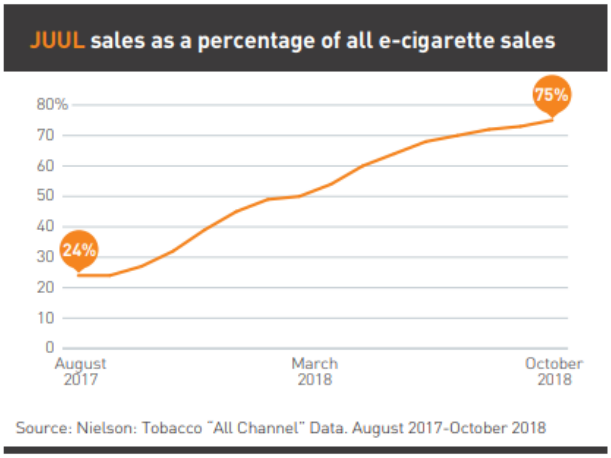
In 2015, a *fourth generation* of ENDS entered the market, disrupting the e-cigarettes landscape through product innovation in both aesthetics and composition. Manufactures of POD-based products include JUUL, Bo, Kwit Stick, Mistic, Rubi, and Suorin products.[4]

Figure 3: POD-based product



JUUL combines a sleek, tech-inspired modern design that resembles a USB-drive (Figure 3) with disposable cartridges (PODs) containing protonated (salt-based) nicotine from leaf tobacco.[3] The use of protonated nicotine—unique to JUUL and other POD-based products—greatly reduces airway irritation compared with the freebase nicotine used in other ENDS and also in cigarettes,[3] allowing high levels of nicotine to be inhaled with relative ease.[5] JUUL has been central to the sharp increase of ENDS use among youth, which will be discussed later in this brief.

Figure 2: JUUL sales growth



JUUL is by far the leader in sales of POD-based products and has gained rapid popularity in a very short period of time: by 2018, JUUL had 75% of the entire ENDS market share (Figure 4).

What is in JUUL? According to its manufacturer (https://www.juul.com/learn/pods) JUUL pods contain nicotine in protonated form, propylene glycol, glycerin, and flavor, described as "naturally occurring and artificial flavor ingredients which provide the specific taste profile for each flavor." JUUL also contains benzoic acid, "a naturally occurring ingredient, found in tobacco and other substances." It is not clear from the JUUL manufacturer's description if the benzoic acid used in their pods comes from tobacco plants or from other substances.

Health Risks of ENDS Use: What Do We Know?

Scientific knowledge is lagging behind the rapid uptake of ENDS, as documented in recent reviews of the literature.[1,5,6] It will take decades to achieve a solid body of knowledge about ENDS that can be compared to what it is known about the health consequences of traditional tobacco use. This section presents some of the short and long-term consequences of ENDS use, taking into consideration some specific chemicals used in ENDS e-liquid and risks associated with device malfunction.



Short-term health risks

There is clear evidence that ENDS can cause injury due to battery malfunction of some devices.[1] Between 2012 and 2015, 47 people were injured due to explosion, overheating, and fire caused by ENDS; some of these injuries were permanently disabling.[6,7] A recent study analyzing social media posts on the topic between 2013 and 2017 suggest that this event, while rare, continues to be an issue.[8]

ENDS use may also cause cough, throat irritation, dizziness, and some light headiness, none of these considered serious adverse health events.[6] Accidental or intentional exposure to e-liquids has caused eye and skin irritation, nausea, and vomiting in both children and adults. [9,10]

There is limited evidence that ENDS use is associated with short-term increase in blood pressure, arterial stiffness, changes in biomarkers of oxidative stress, and increased endothelial dysfunction.[1]

Long-term health risks

There is a dearth of research on the long-term health risks of ENDS use and high interest in the scientific community to advance knowledge about this new public health phenomenon. Research on ENDS' possible long-term health risks in humans can be extrapolated from studies with animals or research into the specific components of e-liquids.

Propylene glycol (PG) and glycerol (GL): PG and GL are present in unknown quantities and ratios in every ENDS e-liquid available in the market to date. While both products are generally considered safe for ingestion, there are almost no studies of their safety for long term inhalation.[11] The little that is currently known suggests significant health consequences from inhaling PG and GL. A study conducted with e-juice vaporized in ENDS using tank-systems found that some molecules are converted to formaldehyde-releasing agents when PG and GL are heated to high temperatures in the presence of oxygen.[12] While it is not known how this chemical behaves in the respiratory tract, formaldehyde is classified as a group 1 carcinogen.[12] Similarly, the formation of benzene, an important human carcinogen, was detected in some ENDS using tank systems, formed from heating PG and GL especially at high power settings.[13]

Flavoring: There are more than 7,000 unique e-liquids in the market. E-liquids are generally recognized as safe (GRAS) for oral consumption in food by the Food and Drug Administration (FDA); however, most of these were never studied for toxicity via the inhalation route.[1] Flavoring composition is proprietary, making it challenging to determine a risk profile specific to each flavor. Some examples of possible risks involve the use of diacetyl, a flavoring chemical found in 39 of the 51 flavors tested in a recent study. Diacetyl exposure is associated with *bronchiolitis obliterans* or "popcorn lung."[14] The presence of ethyl maltol in some JUUL pod flavors is high enough to be cytotoxic in *in vitro* assays.[15] Another study measured the effects of ENDS aerosols on tissues and cells of animal lungs and found that exposure to some e-cig aerosols/liquids—particularly those containing sweet or fruity flavors—resulted in measurable oxidative and inflammatory responses in lung cells and tissues, considered key events in the development of chronic airway diseases.[16]

Nicotine: Nicotine is a stimulant, increasing both blood pressure and heart rate. It is also very addictive. The 4th generation of ENDS delivers nicotine in its protonated form, which makes it possible to deliver very high amounts of nicotine with minimal throat and respiratory tract irritation. One JUUL pod has the same amount of nicotine as one cigarette pack (20 cigarettes), maximizing nicotine addiction potential.

ENDS Potential for Harm Reduction and as a Cessation Tool for Smokers

While scientific knowledge clearly demonstrates that ENDS products are not harmless, they are less harmful than smoking cigarettes, and therefore may have some public health value. In its comprehensive 2018 review of the literature on e-cigarettes[1], the National Academies of Sciences, Engineering and Medicine (NAS) confirmed ENDS' utility and found "conclusive evidence that completely substituting e-cigarettes for combustible tobacco cigarettes reduces users' exposure to numerous toxicants and carcinogens present in combustible tobacco cigarettes" (p. 11) and also "substantial evidence that completely switching from regular use of combustible tobacco cigarettes to e-cigarettes results in reduced short-term adverse health outcomes in several organ systems" (p. 11). It is noteworthy that these benefits are only valid if there is a complete substitution of products—there is no evidence that dual use of cigarettes and ENDS can bring any health benefit.

Another potential benefit—claimed by ENDS companies—is that they are a tool for smoking cessation. An online survey of JUUL users, funded by JUUL, found that 28.3% of adults who used JUUL for three months reported no use of tobacco cigarettes for at least 30 days.[17] This finding should be viewed with caution, not only because it was funded by an ENDS company[18] but also because is not confirmed by the National Academies of Sciences appraisal of the literature, which concluded there is limited evidence that e-cigarettes can help smokers quit. The NAS report notes that

results of trials and observational studies often differ, and very little data from randomized controlled trials substantiate a positive role of ENDS in smoking cessation.

Another aspect to consider is that ENDS' role in smoking cessation may depend on the societal context where its use takes place. A 2019 study from the United Kingdom, not included in the 2018 NAS review, conducted a randomized trial of adults seeking help to quit smoking through UK National Health Services comparing two groups: one group had four counseling sessions plus nicotine-replacement therapy (NRT); the other had four counseling sessions plus a second generation ENDS starter kit. They found an 18% abstinence rate among participants in the ENDS group one year later, compared to 9.9% in the NRT group.[19] This encouraging result should be seen in the context of UK tobacco cessation policies: ENDS are regulated as medicinal products by the UK Medicines and Healthcare products Regulatory Agency (MHRA), an agency equivalent to the US FDA;[26] their advertising is severely restricted; and their sales outside the health services system is regulated and limited.[20] This context is very different from the US landscape, where ENDS have not been analyzed or regulated by the FDA to date and are widely marketed and available online and in many retail stores.

> Nicotine vaping among youth increased significantly in WA State, from 2016 to 2018. This increase mirrors national trends and has been attributed to the rapid rise in popularity of JUUL e-cigarettes. In 2018, 10.5%, 21.2% and 29.6% of 8th, 10th, and 12th graders in Washington State reported using e-cigarettes in the last 30 days.[26]

In the United States health and tobacco policy landscape, there is not enough evidence to suggest that e-cigarettes offer a comparable or better alternative to more established smoking cessation tools such as NRT.[1]

ENDS Use Among Youth: Public Health Concerns

The National Academies of Sciences, Engineering, and Medicine reports substantial evidence that e-cigarette use increases the risk of ever using combustible tobacco cigarettes among youth and young adults.[1] This finding seem to hold true across numerous age groups and even for youth who are at low risk for tobacco use, such as youth who do not have friends who smoke.[1,21] For youth who report ever using combustible cigarettes, using ENDS products might increase the frequency of combustible cigarette smoking.[1] Youth who use ENDS products but do not transition to other forms of tobacco use are not free from harm. According to the 2018 *Surgeon General's Advisory on E-cigarette Use Among Youth,*[5] youth and young adult use of nicotine can adversely affect brain development, in turn impacting cognitive realms of learning, memory, and attention. [5]

Of particular concern is that youth may falsely believe that they are using a nicotine-free product. One study, using data from 2017 and 2018, compared youth self-report of nicotine through ENDS products with participants' urinary biomarkers, and found that 40% who reported using nicotine-free products had significant amounts of cotinine (a biomarker for nicotine exposure) in their urine.[22] This finding seems to hold true for youth who use JUUL, a product that always contains nicotine and does not contain a flavor-only option in the market. One study found that 63% of JUUL users aged 15-24 believed that JUUL cartridges contained no nicotine.[23] In fact, a JUUL pod on average contains as much nicotine as found in 20 cigarettes.[5] According to 2017 data, JUUL is among the most currently-used ENDS product among youth, with 47.1% of participants reporting current JUUL use.[24] Reported current use of other ENDS were: MODS (33.1%), vape/hookah pens (18.7%), and cig-a-likes (7.3%).[24] As mentioned previously, JUUL's design and utilization of a nicotine salt rather than freebased nicotine results in a smoother sensation, allowing users, adult and youth alike, to inhale more vapor (and thus, more nicotine) with each pull.[3]

Final Considerations

There is no certainty about the future complex and fast-evolving role of ENDS products on the health of the American people. It is, however, possible to estimate effects of e-cigarettes at a population level, using complex "dynamic modeling" techniques.

The National Academy of Sciences committee used this method to forecast e-cigarettes' impact on population health, taking into account the possibility of e-cigarettes harming some groups (e.g., youth who initiate tobacco), while

benefiting others (e.g., adulst who reduce or completely quit smoking). Their model assumed that ENDS would be responsible for a smoking *initiation* rate of 10% or more, and an additional smoking *cessation* rate of 5-15%.

Under these assumptions, their model suggests that ENDS use will generate a net public health benefit, at least in the few next decades. They also note that "…harms from increased initiation by youth will take time to manifest, occurring decades after the benefits of increased cessation are seen." In the long term (e.g., 50 years out), projections suggest that the net public "health benefit is substantially less and is negative under some scenarios."

In any scenario, what we do as a society in terms of instituting policies and practices to protect public health is likely to make a big difference. To maximize the chances of a societal net benefit of these new products, the report suggests policies and actions to discourage ENDS use among youth, increase ENDS safety through data-driven product engineering and design, and determine with more precision whether and under which conditions e-cigarettes could serve as an effective smoking cessation aid.

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