THE ROLE OF FLAVORING IN TOBACCO HARM REDUCTION

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EXECUTIVE SUMMARY

One of the great public health controversies of our time surrounds the debate over what role Electronic Nicotine Delivery Systems (ENDS), of which e-cigarettes are the most common type, might play in tobacco harm reduction. A key element of this discussion concerns the role of flavorings.

Regular users of ENDS declare that flavor is important in their ability to cease smoking. In the absence of flavors to soften the sometimes-harsh taste of nicotine vapor, they are likely to resume smoking cigarettes.

Some public-health officials have expressed concern that certain flavors might attract young people to experiment with nicotine at an early age. Evidence for this thesis has not yet been demonstrated. Concerns about the safety of ENDS and whether ENDS might attract young people to nicotine use threaten to dominate what should be a far broader discussion about how tobacco-harm-reduction strategies could be used to improve public health.

INTRODUCTION

There are 42 million smokers in the United States. On average, they will live 10 fewer years than their nonsmoking peers. Although roughly 70 percent of U.S. daily cigarette smokers say they want to quit, fewer than half will attempt to do so in a given year. The long-term success rate of these quit attempts is about 6 percent.

M. Bradley Drummond of Johns Hopkins University School of Medicine has estimated that at least 36 million U.S. adults are unwilling or unable to abstain completely from combustible cigarettes. If a substantial number of smokers switched to ENDS, the impact on death, disease and the cost of health care would be profound.


In the debate around ENDS within the public-health community, the first question goes to the very nature of harm-reduction interventions: should they be entirely free of harm? A recent article in Science reviewed the rancorous dialogue among clinicians who argue either side of this question. Scholars agree that the differences between combusted smoke and vapor are substantial, but to some, any nicotine, or any chemical, is inherently harmful. A recurrent theme of the arguments used by those who oppose ENDS as a harm-reduction strategy is a strong distrust of tobacco business interests, with some stating flatly that nothing the tobacco industry says is to be believed.

Sometimes, this anti-industry posturing is quite intentional. Amy L. Fairchild of the Columbia University Mailman School of Public Health has explored the role of fear-based education programs in several public-health campaigns. The Centers for Disease Control and Prevention (CDC), public-health authorities and interested media frequently have exaggerated reports of e-cigarettes’ possible toxicity. Michael Siegel, a professor at the Boston University School of Public Health, has documented many such examples. Demonization of the tobacco industry and of all nicotine products as equally harmful becomes a recurrent “theme amplifier” of general health messages and reduces the opportunity to form consensus around shared public-health goals.

A second question in the debate concerns the threshold of proof needed to justify implementing a harm-reduction strategy. How much evidence is required to support use of a specific intervention? The contrast between the approach taken in the United Kingdom and the United States is revealing. This past spring, Public Health England issued a review of the health and safety implications of electronic cigarettes that concluded their use is about 95 percent safer than smoking.

The authors conclude that smokers who have tried other methods of quitting without success could be encouraged to switch to e-cigarettes. In addition to encouraging their use as a cessation tool, encouraging switching could help reduce smoking-related disease, death and health inequalities.

In the United States, that same evidence has been subject to radically divergent interpretation. The U.S. Preventive Services Task Force’s recently updated clinical-practice guidelines concluded there is insufficient evidence to support the use of ENDS in smoking cessation. For its part, the CDC has conducted a very aggressive public-relations campaign against ENDS, even though a close reading of available public-health information would counsel a nuanced understanding of the devices’ health potential. A recent fact sheet distributed by the CDC stated:

In order for adult smokers to benefit from ENDS, they must completely quit combusted tobacco use. Smoking even a few cigarettes per day is dangerous to your health.

While this statement could be read as supportive of ENDS as a harm-reduction strategy, it fails to take into account that any reduction in combusted smoke would be a positive. The overwhelming thrust of the CDC’s public-relations campaign has been vehement opposition to nicotine use in any form. For example, earlier this year, the agency trumpeted findings that “e-cigarette use among middle and high school students tripled from 2013 to 2014,” without highlighting the very low levels involved or explicating what proportion of use was one-time experimentation and what proportion actually were teens who turned to e-cigarettes to help quit smoking. Clarity in this complex debate requires a nuanced understanding of the components of vapor, nicotine, flavoring and other compounds within the context of how they actually are used and how they can be tested.

NICOTINE SENSITIVITY AND THE YOUNGER BRAIN

It is well-established that the brains of younger persons are more vulnerable to alcohol, drugs and nicotine. The brain continues to mature into one’s mid-20s. The younger the age of onset of any drug use, the greater difficulty the subject will

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11. Ibid.
face in trying to quit. This is especially true for smoking.\textsuperscript{15}

The earlier nicotine use is initiated, the more difficult it is to cease later in life. As a result, there’s near-universal agreement on the need to prevent ENDS sales to people under age 18.

Another interpretation of the same data might suggest that people with higher vulnerabilities start experimenting with nicotine and other drugs at earlier ages. Although a high proportion of young people experiment with nicotine, only a modest fraction adopt regular use. Self-medication with nicotine could explain much of the observed continued smoking in young people.\textsuperscript{16} The significance of this observation can’t be underestimated, as more than 50 percent of all cigarettes consumed in the United States are smoked by people with one or more mental-health diagnoses.\textsuperscript{17}

\textbf{THE IMPORTANCE OF FLAVORING}

Detailed study of smoking behavior shows that smokers’ typical patterns of cigarette use help to maintain a relatively constant level of nicotine throughout the day.\textsuperscript{18} The same would be true of vapers.

The mechanisms by which ENDS and cigarettes each deliver nicotine to the lungs differ fundamentally in both process and outcome. The delivery of nicotine varies by device type, but measured nicotine levels in the blood of vapers show that ENDS consistently deliver lower levels than cigarettes. Additional puffs are required to sustain constant levels of nicotine.\textsuperscript{19} It is now well-established that, puff-for-puff, cigarettes deliver more nicotine than most ENDS.\textsuperscript{20} Vapers compensate for the reduced availability of nicotine by taking in a larger number of puffs.

Vapers generally report their motivations are harm reduction and smoking cessation, and that they are well-aware that ENDS use is not completely safe.\textsuperscript{21,22,23} More than half of users who responded to a large international Internet survey – with a sample size of 19,000 – reported symptoms that they attributed to ENDS; dry mouth and throat were the most common.\textsuperscript{24} Given these issues, and the relatively greater number of puffs that ENDS users must make to obtain a comparable amount of nicotine, it’s perhaps unsurprising that blogs and other websites geared toward the vapor community are filled with thousands of narratives about the significance of flavor. Some examples culled from the Internet include:

- ‘I will celebrate my two year tobacco free. Due to quality flavors. Yes I use a Baked Cinnamon Roll, Strawberry Milk, Blue Raspberry, Blueberry fruits, Butter-scout candy flavors...’\textsuperscript{25}

- ‘BTW I’m 46 years old and I love the candy flavors, the bakery flavors and all the other things supposedly only kids are suppose to like and do not care for any of the tobacco flavors at all. I really wish people in general against these types of flavors and who create such ridiculous lies and false assumptions about them using “The Children” as an aid to fight vaping would stop insulting the intelligence of the people of the world about this topic. The fact is whether you a baby or over 100 years old and can still taste age has nothing to do with what tastes good to an individual but it is a major part of what keeps people from going back to smoking.’\textsuperscript{26}

- ‘My very first juice I used was menthol tobacco flavor to help ease the transition. I have since only used fruity flavored juice as the tobacco juice smell also makes me sick. The different flavors have helped. It’s like having a ham and cheese sandwich to eat everyday for months... you get sick of eating ham and cheese. The

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\textsuperscript{18} Neal L. Benowitz and Jack E. Henningfield, “Establishing a nicotine threshold on the need to prevent ENDS sales to people under age 18.


different flavors are to help keep people from getting sick of the same flavor and giving up on it.27

Large-scale surveys of vapers show many users vary the use of flavors throughout the day. Konstantinos E. Farsalinos, a research fellow at Greece’s Onassis Cardiac Surgery Center, conducted an Internet-based study of 4,618 ENDS users and found that 63 percent vary their flavors on a daily basis.28 The significance of flavoring was further confirmed in a study of posts on ENDS flavors made to the news and social networking site Reddit.29

SAFETY OF ENDS FLAVORING

ENDS products contain varying amounts of nicotine, but the greatest source of variation is flavoring. When ENDS users visit a vape shop, they generally have a selection of several hundred to several thousand flavors from which to choose. For the most part, these are well-established chemical products that have already entered the marketplace as additives to food. Most already fall under the classification of “generally regarded as safe”30 as defined by Food and Drug Administration guidelines:

If a substance is not generally recognized as safe by qualified experts for its Intended use in food and does not qualify for any of the other exemptions from the food additive definition, it is a food additive. Many substances intentionally added to beverages and other conventional foods are food additives. Food additives require premarket approval based on data demonstrating safety. Usually, these data are submitted to us in a food additive petition, although we may also approve a food additive on our own initiative without first receiving a petition.

But while many of the flavorings meet GRAS standard as food additives, there have been no petitions regarding their use as inhalants. Furthermore, not enough is known about the changes that occur when these chemicals are heated in an ENDS. The FDA also does not have equivalent standards for GRAS for inhaled materials; oversight of inhaled substances has focused on the effective delivery of pharmacologic agents. On occasion, there has been discussion of the safety of propellants used to deliver aerosols, but the safety of inhaled flavorings has not been subject to extensive research. Concerns about the safety issues associated with flavorings have been debated in the medical literature, but little progress has been made to provide any measure of scientific certainty.31

Some researchers, such as Jessica Barrington-Trimis of the University of Southern California Tobacco Center of Regulatory Science, have pointed to the number and variety of delivery devices and flavors as part of a call for more extensive regulation:

As of January 2014, there were 466 distinct brands of electronic nicotine products and at least 7,764 unique flavors, an increase of about 10.5 brands and 242 new flavor products per month from August 2013 to January 2014.32

A recent article about a food flavoring used in some ENDS represents how information about possible harm associated with vapor becomes exaggerated in the media. In December 2015, the Wall Street Journal published an article headlined “Study Finds E-Cigarettes Contain Chemical Tied to ‘Popcorn Lung,’” which bore the subhead:

Harvard researchers say 39 of the 51 flavors sold by leading brands contained diacetyl, which has been linked to severe respiratory diseases.33 The original article, published in Environmental Health Perspectives and authored by a team led by Joseph G. Allen of Harvard University’s T.H. Chan School of Public Health, argues that diacetyl is present in some ENDS flavors to create the taste of butter.34 Allen goes on to argue that the chemical’s presence represents a source of harm to all ENDS users. High levels of acetyl was associated with the occurrence of

32. Barrington-Trimis, et al., 2014
33. Konstantinos E. Farsalinos, Kurt A. Kistler, Gene Gillman and Vassilis Voudris, “Study Finds E-Cigarettes Contain Chemical Tied to ‘Popcorn Lung,’” which bore the subhead: “Study Finds E-Cigarettes Contain Chemical Tied to ‘Popcorn Lung,’” which bore the subhead:
34. Barrington-Trimis, et al., 2014
a serious lung disease among workers who produced butter-flavored popcorn. A small number of workers, exposed without environmental control or personal protective equipment, went on to require lung transplants. The association of acetyl and so-called "popcorn lung" is still under debate in the literature. Writing about the paper on his blog, Michael Siegel has noted the quantities of acetyl measured in cigarette smoke is 750 times greater than that in e-cigarette vapor.

The complexities of evaluating all of these delivery systems and flavors is daunting, especially when one considers that the flavorings are heated and further interact with other compounds. Research on the many compounds contained in ENDS products continues in many settings. However, assembling a sufficiently comprehensive data set may prove overwhelming.

**ENDS AND ‘CHILDREN’S FLAVORS’**

The availability of, e.g., “bubble gum” and “watermelon” flavors has been taken by some as a sign that ENDS producers seek to attract young people to experiment with nicotine, an extension of the thesis that tobacco companies seek to addict new generations of users. Concern about flavorings dates back to early tobacco-control efforts and specifically those efforts to stamp out targeted marketing to children. The Family Smoking Prevention and Tobacco Control Act went on to require lung transplants. The association of acetyl "sour," grape, green apple and “multiple flavor.”

Flavoring frequently is taken into account to facilitate adherence to medical treatment, with a substantial literature on flavorings for over-the-counter medications for both children and adults. For example, Children’s Tylenol is available in “cherry blast” and grape flavors. It also should be noted that nicotine gum and lozenges generally are available in mint, cherry, cinnamon and other flavors.

Michael Shiffman of the University of Pittsburgh examined interest in e-cigarettes among nonsmoking teens and adult smokers, and the effect of offering e-cigarettes under various flavor descriptors. The results did not support the conclusion that adding flavors to ENDS would attract nonsmoking teens. A review of the literature on flavor in a broad range of tobacco products by Shari P. Feirman of the Schroeder Institute for Tobacco Research and Policy Studies concluded that flavored tobacco use is, in fact, associated with younger smokers. However, there is no data showing that young people are specifically drawn to what often are characterized as “children’s flavors.”

**Discussion of the effect of flavoring on children also can be easily misrepresented.** A team led by Bridget K. Ambrose of the Johns Hopkins Bloomberg School of Public Health studied 13,000 teenage users of tobacco products, who were asked about their first experiences. The press interpreted

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the study as demonstrating that “first-time tobacco users” are “lured by flavors,”47 with Ambrose herself reporting:

[T]he majority of youth ever-users reported that the first product they had used was flavored, including 88.7% of ever hookah users, 81.0% of ever e-cigarette users, 65.4% of ever users of any cigar type, and 50.1% of ever cigarette smokers.

However, those finding should not be taken to mean that flavor itself was responsible for youths’ decision to try tobacco products. It is as likely that most of the choices for nicotine use that are available to young people are flavored.

It may be important to consider the context in which young people may be tempted by flavor. A visit to a local newsstand shows an assortment of heavily marketed brands in familiar brightly colored packages. Compare this to the vape store experience, where a much larger assortment of products and containers are on display, few with recognizable names or packaging. Moreover, most ENDS merchants are reluctant to allow children in their shops at all and many communities have specific restrictions on sales to minors.48

OTHER INGREDIENTS OF NICOTINE VAPOR
There are approximately 600 ingredients in cigarettes which, when burned, produce more than 7,000 chemicals. At least 69 of these chemicals are known to cause cancer and many are poisonous.

The chemical composition of nicotine vapor is less well-documented, given the large variation in sources and delivery systems. Common elements include water, nicotine, glycerin, propylene glycol and flavorings, all of which are heated to several hundred degrees. To the extent that some brands have been studied, the consensus is that the number of toxins and carcinogens is substantially smaller than in combusted cigarettes, as is the concern about their concentration.

In its fact sheet on ENDS, the CDC states:

ENDS generally emit lower levels of dangerous toxins than combusted cigarettes. However, in addition to nicotine, ENDS aerosols can contain heavy metals, ultrafine particulate and cancer-causing agents like acrolein. ENDS aerosols also contain propylene glycol or glycerin and flavorings. Some ENDS manufacturers claim that the use of propylene glycol, glycerin, and food flavorings is safe because they meet the FDA definition of ‘Generally Recognized as Safe.’49 However, GRAS status applies to additives for use in foods, NOT for inhalation. The health effects of inhaling these substances are currently unknown.

A comparison of the toxic elements contained in ENDS vapor with those contained in cigarette smoke shows the majority of harmful compounds are absent. Where they are present, toxins in ENDS are at far lower concentrations.

Notwithstanding these uncertainties, public-health authorities concede that ENDS are probably safer than cigarettes, despite those same authorities’ reluctance to recommend them. The first major challenge to earning acceptance from the public-health community is acquiring better understanding of the extraordinary proliferation of ENDS products and flavorings in an entirely unregulated marketplace.

ENDS products have been available for more a decade. There have not, to date, been reports of clinical syndromes associated with ENDS use. News reports have focused on fire dangers associated with some types of devices and the Transportation Safety Administration has required that travelers stow ENDS devices on their person or in carry-on baggage – not in checked luggage that would be stored in cargo holds.50 Also of concern have been poisoning risks associated with children or household pets who accidentally ingest nicotine e-liquids.51

The absence to date of evidence of adverse health outcomes does not prove the long-term effects of ENDS device use is minimal. But consumer behavior has been a positive sign. A recent Reuters poll concluded that 10 percent of the adult population uses ENDS alone or together with cigarettes.52 Two recent studies of practicing physicians find that half report their smoking patients ask about e-cigarettes and one out of three of these physicians recommend their use for harm reduction or cessation.53,54

49. Volk, et al., 2015.
CONCLUSION

Notwithstanding broader concerns about ENDS, their use as a strategy for smoking cessation and harm reduction is now very common. In order to reap the benefits of harm reduction, public-health authorities in the United States might consider an approach more in line with that taken in the United Kingdom. This would require a greater focus on the harm-reduction possibilities of smokers switching to ENDS, rather than excessive scrutiny of the residual risks inherent in ENDS.

In this larger context, concerns about the use of flavoring as a tool to recruit children are overblown. There are no “kid’s flavors,” per se, nor is there any evidence that children are drawn to tobacco products specifically because of flavor. Restricting the sale of nicotine products to people over the age of 18 should address most concerns regarding the effect of nicotine on younger brains. ...

Although there remains insufficient information about the full range of flavoring additives, until demonstrated to the contrary, most flavorings used in ENDS should be considered safe relative to the risk of smoking combusted tobacco.

A great deal of additional research is required to resolve many of the possible safety questions regarding ENDS. But surveys of smokers who already are using the products to cease an unquestionably deadly habit demonstrate that the public has already made up its mind on the matter.

ABOUT THE AUTHORS

Dr. Edward Anselm is medical director of Health Republic Insurance of New Jersey and a senior fellow of the R Street Institute.

Edward is a frequent speaker at population health conferences and has been a strong advocate for reimbursement of smoking-cessation services. Most recently, he implemented the first harm reduction strategy sponsored by a health plan. Building on reimbursement for smoking cessation and enhanced coverage of FDA-approved smoking-cessation medications, the program seeks to engage patients and their doctors in a dialogue about harm reduction.

He previously served as chief medical officer of Freelancers Health Service Corp/Health Republic Insurance of New York, HIP Health Plan and Fidelis Care of New York. As a health care executive, his focus has been implementation of disease management and case management programs.

Trained in internal medicine at the Rosalind Franklin University of Medicine and Science, Edward for several years ran a primary-care clinic. During his residency at Montefiore Medical Center, initiated a smoking cessation clinic. Since then, he has organized and led a number of clinics at hospitals and in workplace settings.

Edward is a fellow of the New York Academy of Medicine and serves on the board of the New York-metro chapter of Physicians for a National Health Plan. He also teaches courses on tobacco control and other public health topics as an assistant clinical professor of medicine at the Icahn School of Medicine at Mount Sinai.