**Provider Materials: Annotated Version**

This document provides a more detailed review of additional evidence (in blue) to support the information already provided in the provider handout. Additional references are also listed (see “Additional References”, also in blue).

*Text Last Updated: 2/6/2017*

**Title:**

E-Cigarettes & Your Patients

**Summary:**

Despite the rising popularity of electronic cigarettes (e-cigarettes), there is confusion regarding their effects on health and role in smoking cessation. There is increasing evidence that e-cigarettes have a serious negative impact on both personal and public health. You can play a key role by discouraging nicotine use and encouraging patients to utilize FDA-approved smoking cessation methods, not e-cigarettes.

**About E-Cigarettes:**

E-cigarettes are devices that deliver a nicotine-containing aerosol for inhalation. While there is extensive variation in the composition of e-cigarette liquid, the main components are:

**Nicotine:**

E-cigarettes are capable of delivering equal or greater amounts of nicotine compared to conventional cigarettes1.

One study analyzing the effectiveness of nicotine delivery for e-cigarettes found that e-cigarettes delivered an average of 1.3 mg (range 0.4–2.6 mg) of nicotine from 15 puffs, similar to or higher than average reported yields of 0.5–1.5 mg nicotine per tobacco cigarette (St. Helen, PMID: 26430813).

Human and animal data support that nicotine exposure, especially during developmental periods, can have multiple adverse health consequences2.

Nicotinic acetylcholine receptors (nAChRs) play a role in regulating brain development, and fetal exposure to maternal smoking has many known health risks, including an increased likelihood of developing sudden infant death syndrome (SIDS) (Dwyer, PMC2746456). In human studies, smoking during adolescence is associated with problems in working memory and attention, and additional studies in animal models show clear changes in prefrontal cortical circuitry in response to nicotine exposure during development. (Goriounova, PMC3543069)

**Flavorings:**

There are over 7,000 flavors of e-cigarettes, many of which are designed to appeal to children and contain known toxic chemicals. These include diacetyl, which causes “popcorn lung,” and compounds that lead to other chronic respiratory and cardiovascular diseases3,4,5. Flavoring chemicals exist even in traditional flavors such as “classic” and “menthol.”3

As of January 2014, a comprehensive online search of e-cigarettes yield over 450 unique brands and a total of over 7,000 different flavors (Zhu, PMID: 24935895).

Flavors have marketed to children and young adults by using bright childlike packaging (Fig. 1) and by giving them appealing names such as Cotton Candy, Tutti Frutti, Alien Blood, Waikiki Watermelon, Blue Water Punch, etc. ([PMC4892929](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4892929/)). Diacetyl and other flavoring compounds have been have been marked by the FDA as Gernerally Recognized as Safe (GRAS) for ingestion, diacetyl is not safe for inhalation (<https://www.cdc.gov/niosh/topics/flavorings/exposure.html>).

In the early 2000s, many microwave popcorn workers exposed to arosolized diacetyl were found to have developed “popcorn lung”, an irreversible loss of pulmonary function whose only treatment is a lung transplant ([PMC4892929](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4892929/)). Other compounds such as formaldehyde, acetaldehyde, acetone, acrolein, and butanol have been detected in E-cigarettes. Formaldehyde inhalation has been shown to cause oxidative stress on the heart as well as reduce cardiac contractility and heart rate (Citation 4. Bhatnagar).

The breakdown products of flavoring compounds often include acrolein, which has been implicated in vascular pathogenesis (Yousefipour, PMID 19633273).



A) B)

Figure 1 - E-Liquids Advertised Using Children’s Cereal. A) One Hit Wonder Police Man E-Liquid advertised with Lucky Charms Cereal and sold on LighterUSA.com. B) Trickz E-Liquid advertised with the Tricks Cereal mascot and sold by ejuices.com.

**Vegetable glycerin/propylene glycol:**

Although used in some consumer products, little is known about the safety or carcinogenic effects of these substances when heated, aerosolized, and inhaled.6

“Inhalation of the vapors of propylene glycol may present no significant hazard in ordinary applications, but limited human experiences indicate that its mists may be irritating to some individuals [Dow Chemical, 2006].” In animal studies, though, inhalation of propylene glycol has both reproductive and developmental effects. (https://www.atsdr.cdc.gov/toxprofiles/propylene\_glycol\_addendum.pdf)

Heating up the components of e-cigarettes produces formaldehyde and other toxic aldehydes.

It is important to note that the content of e-cigarette liquid is highly variable, and even the labeled nicotine levels can be inaccurate.

In Allen et al., products from companies promoting zero diacetyl in their e-liquids tested positive for diacetyl. Furthermore, a North Dakota study found that 51% of labels on e-cigarette liquid nicotine containers do not accurately reflect the actual levels of nicotine found in the products, with one example of product which contained 172% more nicotine than the labeled quantity (Buettner-Schmidt, PMID 27079973).

The FDA has authority over e-cigarette manufacturing, but is not yet actively regulating them.

Although the FDA has extended its regulatory authority to all tobacco products (including e-cigarettes) as of August 8, 2016, it expects that manufacturers will continue selling their products for up to two years while they submit—and an additional year while the FDA reviews—a new tobacco product application (FDA, http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm506676.htm#timeline). As a result, quality control is not yet enforced and the levels of nicotine, tobacco-specific nitrosamines (TSNAs), aldehydes, metals, volatile organic compounds (VOCs), flavors, solvent carriers, and tobacco alkaloids in e-cigarette refill solutions, cartridges, aerosols and environmental emissions vary considerably (Cheng, PMID: 24732157).

**Clinical Guidance:**

1. Ask all patients broadly about tobacco and nicotine use.

An increasing number of youth use e-cigarettes: From 2011 to 2015, use among high schoolers increased from 1.5% to 16%,7 with substantial use among new smokers.8

The U.S. Surgeon general reported that in 2015, 1 in 6 high school students used e-cigarettes in the last month (https://e-cigarettes.surgeongeneral.gov/). Furthermore, more high schoolers today use e-cigarettes than conventional cigarettes.

Use more inclusive language when speaking with patients*:* For example, “In the past 30 days, have you ever used a tobacco product or used any other nicotine-containing product, such as an e-cigarette or vape pen?”

Smoking patterns in the US among young adults have shifted to light, intermittent cigarette use (Schane, PMID: 20368531). To better assess for this pattern of use among patients in clinic, it is especially important to ask about smoking use over a period of time, as suggested above.

2. Do not recommend e-cigarettes as a first-line method for smoking cessation.

Every quit attempt should be encouraged: Combine counseling with FDA-approved cessation methods, such as nicotine replacement therapies (e.g., patch, gum, lozenge) or other prescription drugs (e.g., bupropion, varenicline).

Nicotine replacement therapy (in combination with behavioral counseling) has been associated with a significantly higher incidence of any quit attempt in smokers currently unmotivated to quit (Carpenter, PMID: 22123796).

E-cigarettes are not effective for smoking cessation: Smokers who attempt to quit using e-cigarettes are less likely to quit compared to those who use nicotine-replacement therapy or no cessation aid.9

A meta-analysis of 38 studies found that the odds of quitting cigarettes was 28% lower for individuals who used e-cigarettes compared to those who did not use e-cigarettes (Kalkhoran, PMID:26776875).

Patients who insist on using e-cigarettes should commit to quitting cigarettes: The dose response curve for cigarette use and cardiovascular disease is nonlinear and “cutting back” does not substantially decrease risk.10

3. Provide counseling to patients who use e-cigarettes but have no intention to quit.

E-cigarettes are not harmless: Many patients believe e-cigarette aerosol is harmless water vapor, but they should know it contains nicotine, flavorings, and other dangerous chemicals.

E-cigarette bottles pose a household danger: Cartridge spills, skin exposure, and unintended ingestion can be dangerous for children.

Calls to poison control centers for e-cigarette exposures are increasing dramatically and now make up more than 40% of all tobacco-related calls.11

According to the CDC’s Morbidity and Mortality Weekly Report, the number of e-cigarette calls increased from one per month to 215 per month over an approximately four year period (September 2010 and February 2014). This same trend was not observed for conventional cigarettes. (https://www.cdc.gov/media/releases/2014/p0403-e-cigarette-poison.html)

Importance of a smoke-free home: People who smoke only outside consume fewer cigarettes and have higher rates of quitting.12

In a review that examined the population-level association of smoke-free homes with adult smoking behavior, there was “consistent population-level evidence that a smoke-free home is associated with increased smoking cessation and decreased cigarette consumption in adult smokers”. These studies were predominantly conducted in the United States and similar countries like Australia and Canada.(Mills, PMID 19633273).

In addition, nonsmokers are at risk of absorbing nicotine from passive exposure to e-cigarettes, even without the production of sidestream aerosol.13, 14

Use of e-cigarettes has already been shown to change air quality within a room, by increasing the concentration of particulate matter, volatile organic compounds, and polycyclic aromatic hydrocarbons (Schober, PMID: 24373737). In a systematic review of both human and animal studies analyzing the potential health risks of e-cigarette exposure, there was evidence to suggest that bystanders were impacted by exposure to e-cigarettes despite some study limitations (Hess, PMID: 27734060). In one particular observational study, which looked at 54 non-smokers, cotinine levels, a marker of nicotine exposure, were elevated in non-smokers from home where either e-cigarettes or conventional cigarettes were used (Citation #12)

**Additional Resources for Your Patients:**

There are many sources of assistance available to patients who want to quit smoking:

* **California Smokers' Helpline (free)**: (800) NO-BUTTS;

[www.nobutts.org](http://www.nobutts.org/)

* **UCSF Fontana Tobacco Treatment Center**: (415) 885-7895; [www.ucsfhealth.org/clinics/tobacco\_treatment\_center](http://www.ucsfhealth.org/clinics/tobacco_treatment_center)
* **SF VA Smoking Cessation Programs**: (415) 221-4810, ext. 2-4922;

[www.sanfrancisco.va.gov/services/smoking.asp](http://www.sanfrancisco.va.gov/services/smoking.asp)

* **ZSFGH Community Wellness Programs**: (415) 206-6074;

[www.sfghwellness.org/programs/tobacco-cessastion/](http://www.sfghwellness.org/programs/tobacco-cessastion/)

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**Additional Sources:**

Additional references listed within the text by first author and PMID.

**Patient Materials: Annotated Version**

This document provides a review of the evidence (in blue) to support the information already provided in the patient handout. References are provided below.

*Text Last Updated: 2/6/2017*

**It’s Not Just Water Vapor!**

*E-cigarettes are not harmless water vapor. They contain nicotine, heavy metals, and other dangerous chemicals.*

A common misconception is that e-cigarette smoke is comprised of only water vapor and nicotine. However, e-cigarette liquid contains nicotine, vegetable glycerin, propylene glycol, and flavoring chemicals. When vaporized, the e-liquid has been found to produce carbonyls; diacetyl, a compound known to cause respiratory disease, most notably “popcorn lung”; aldehydes including formaldehyde, a known carcinogen; volatile organic compounds (VOCs) such as benzene, which is found in car exhaust; heavy metals, such as nickel, tin, and lead, and many more harmful chemicals.1,2

**Secondhand Vapor is Dangerous**

*Other people are exposed to nicotine when you use e-cigarettes. Nicotine from e-cigarette vapor lingers on the walls and furniture.*

E-cigarettes still produce a significant amount of secondhand exposure from vapor which can be harmful to others around the user. A study of indoor air quality at an indoor ECIG event held particulate matter concentrations higher than that of hookah cafes and bars allowing cigarette smoking.3 Additionally, residues of harmful chemicals in the vapor can remain trapped in household surfaces, leading to an additional risk of long-term exposure known as “thirdhand smoke.” E-cigarette vapor has been found to linger on exposed surfaces and thus offers a risk of thirdhand exposure.4

**Unproven to Help You Quit Smoking**

*People who use e-cigarettes to quit smoking are less successful. Use proven methods, like nicotine patches, combined with counseling.*

A meta-analysis of 38 studies found that the odds of quitting cigarettes was 28% lower for individuals who used e-cigarettes compared to those who did not use e-cigarettes.5

**Flavorings are Toxic**

*Many chemicals used to flavor e-cigarettes cause serious health problems, including lung disease and damage to your blood vessels.*

There are over 7,000 flavors of e-cigarettes currently marketed.6 In one study, the authors selected 51 types of flavored e-cigarettes sold by leading e-cigarette brands, focusing on flavors that were deemed appealing to youth. The e-cigarette contents were fully discharged, and the air stream was captured and analyzed for total mass of diacetyl, 2,3-pentadione, and acetoin. Results of their testing are shown below:1

* At least one flavoring chemical was detected in 47 of 51 unique flavors tested
* Diacetyl was detected in 39 of 51 flavors tested
* 2,3-pentadione was detected in 23 of 51 flavors tested
* Acetoin was detected in 46 of 51 flavors tested

Diacetyl and 2,3-pentadione are known to cause negative health effects, including decreased lung function and the severe irreversible lung disease, obliterative bronchiolitis.7 Many young e-cigarette users are at risk of exposure to these flavorings, as the U.S. Surgeon General reports that 85% of e-cigarette users between the ages of 12 and 17 use flavorings.8

The breakdown products of flavoring compounds often include acrolein, which has been implicated in vascular pathogenesis (Yousefipour, PMID 19633273).

**You Don’t Know What You’re Getting**

*E-cigarettes that claim to be nicotine-free may contain nicotine.*

Although the FDA has extended its regulatory authority to all tobacco product, (including e-cigarettes, as of August 8, 2016, it expects that manufacturers will continue selling their products for up to two years while they submit—and an additional year while the FDA reviews—a new tobacco product application.9 As a result, quality control is not yet enforced and the levels of nicotine, tobacco-specific nitrosamines (TSNAs), aldehydes, metals, volatile organic compounds (VOCs), flavors, solvent carriers, and tobacco alkaloids in e-cigarette refill solutions, cartridges, aerosols and environmental emissions vary considerably.10

**They Are Addictive**

*E-cigarettes deliver nicotine, the addictive drug in cigarettes.*

St. Helen et. al measured the systemic retention of nicotine, propylene glycol, and vegetable glycerin in electronic cigarette users and assessed the abuse liability of e-cigarettes by characterizing nicotine pharmacokinetics.11 They found that “E-cigarettes can deliver levels of nicotine that are comparable to or higher than typical tobacco cigarettes, with similar systemic retention. Although the average maximum plasma nicotine concentration in experienced e-cigarette users appears to be generally lower than what has been reported from tobacco cigarette use, the shape of the pharmacokinetic curve is similar, suggesting addictive potential.”

**References:**

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