Internal Medicine Grand Rounds
University of Texas Southwestern Medical Center
January 4, 2019

Vaping: Cleaner Nicotine or New Toxic Epidemic?

Jason Clark MD
Assistant Professor of Medicine
Division of Pulmonary and Critical Care

This is to acknowledge that Dr. Clark has disclosed that he does not have any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Clark will not be discussing off-label uses in his presentation.

Purpose and Overview:

To discuss the current data regarding electronic cigarettes, including their safety and effectiveness as alternatives to traditional smoking, and to discuss the primary care physician's role in counseling our patients regarding these devices.

Educational objectives:

The listener should be able to:

- discuss the trends in growth of electronic cigarette usage, especially with regard to American youth.
- understand the potential toxicity of electronic cigarettes, on their own, and relative to traditional cigarettes.
- have a basic understanding of the components of electronic cigarettes as well as the fluid products used in them.
- identify areas of this topic for which very little is known and which represents an opportunity for future study.
- discuss the conflicting ideas of harm reduction vs renormalization when it comes to nicotine addiction, electronic cigarettes, and smoking.

About the author:

Dr. Clark was born in raised in Dallas, TX. He has lived his whole life in the metroplex except for 4 years of undergraduate education at UT Austin. He earned his MD and completed his residency and fellowship training at UT Southwestern. Following graduation in 2008 he worked as a Pulmonary and Critical Care physician in the Baylor Healthcare system for 5 years. He has returned to Southwestern with renewed interest in housestaff education and caring for the critically ill population at Parkland Hospital.

Introduction:

Electronic cigarettes were introduced to the world in 2004, and since that time have grown considerably in popularity.(1) Their presence in the United States has been hotly debated over the last several years. On the one hand, they seem to represent a less toxic alternative to combustible cigarettes and theoretically could establish themselves as a favorable aid for smoking cessation. However, there is significant concern that they appeal to a larger audience of current nonsmokers, who perceive them to be safe, and therefore may drive overall nicotine addiction to higher levels in the community. In addition to this, the actual long term toxicity of these devices is mostly speculative given the short amount of time they have been available. Interest in these devices increased in the medical literature after the CDC reported in 2013 that electronic cigarette usage had doubled in adolescents over the prior 2 years, reaching an estimated 1.78 million students.(2) Efforts to better study potential toxic effects and/or possible benefits accelerated from that point forward. Additionally, government oversight has started to increase as well, especially in the area of how these devices are marketed and made available to young people. As nicotine has been shown previously to have negative effects on the developing adolescent brain, even staunch supporters of electronic cigarettes appear to agree with finding ways to better restrict access to these devices by the youth in our country. In contrast to this, several countries around the world have banned these devices altogether, choosing a striking tone of conservative caution until more definitive data regarding their use is available.(3)

The purpose of this presentation is to
a) Review the currently available information regarding the toxicity of electronic cigarettes (on their own, and relative to combustible cigarettes)
b) Examine the feasibility of using these devices for beneficial effects, such as smoking cessation
and c) Try to draw some conclusions regarding the Primary Care physician's role on counseling our patients regarding these devices.

Anatomy of an Electronic Cigarette/Vaporizor:

In its most basic form, an electronic cigarette consists of a battery (typically rechargeable) which powers a heating coil. This heating coil applies heat to a wick, which is soaked in liquid "vape juice", converting the liquid into vapor which is then directly inhaled. However, this basic format can have considerable variation, which can in turn lead to some confusion for both consumers and physicians about what is included in the term "electronic cigarette".

Early generations devices closely resembled the size and shape of traditional cigarettes and were marketed as smoking cessation tools. A representative example is pictured below:

Photo courtesy of ecigarettereviewed.com

As can be seen here, the actual device is the size and shape of a conventional cigarette. The liquid to be used is supplied in pre-produced cartridges that are simply plugged in to the device. It comes with a battery charger that is reminiscent of a cigarette pack. The goal in production and marketing at the time seems to have been to approximate the traditional smoking experience as closely as possible. This makes the product primarily appeal to current smokers as either an alternative or aid for cessation.

Over time changes in the industry have led to devices such as the one below to be more commonplace:

Photo courtesy of DHgate.com

This design represents a considerable change in experience. Preloaded cartridges have been replaced by a large tank that the user can fill with the liquid of their choosing. Multiple tanks

can be purchased for a single device, enabling the user to have multiple flavors or various levels of nicotine dosing on hand for quick changing, depending on user preference or mood. Additionally, there are variable voltage settings, resulting in different styles of vapor and/or "throat hit" (the description of the desired burning vs smooth effect of the vapor on the oropharynx). This type of device invites experimentation. Multiple flavors can be used in isolation or mixed together at various temperatures. It no longer even remotely resembles classic cigarettes, and the flavor and experience are more prominently promoted. One can hopefully see that this device has more appeal to a "never smoker" than the original products, and there is concern that it is being marketed as such with some success.(4)

Confounding the situation in discussion of these devices is the nomenclature. The bulk of medical literature appears to refer to all of these together as "electronic cigarettes". However, the lay press, bloggers, and users of these devices seem to only apply that term to early generation devices, now opting for the term "vaporizer" for the newer tank based products. There has been a call to refer to all of these products as Electronic Nicotine Delivery Systems (ENDS). However, that term is also fraught with difficulty, as some users opt for using these devices without nicotine entirely.(4)

E-Liquid

Perhaps more important than the devices themselves, is an understanding of the components of the liquid used to generate the inhaled aerosol. So called e-liquid, e-juice, or vape juice.

Typically 4 components are present (5)

- Propylene glycol
- Vegetable glycerin
- Flavoring
- Nicotine (in varying doses)

The first 2 components are generally considered by vaporizer manufacturers to be nontoxic based on their approved use as food additives. However, as has been pointed out in recent literature, oral ingestion vs inhalation are very different routes of administration. The safety of one does not lead necessarily to the other. In other words, the long term effects on the lungs from inhalation of these substances is not known.

The 3rd component "flavorings" is a catch-all term for the hundreds of different flavors and styles of e-liquids available today, ranging from menthol to cotton candy and everything in between. It is difficult to account for all the potential effects of the numerous flavorings being used, especially when some are combined by the end user to varying degrees. Rigorous scientific data regarding the inhalational effects of all of these various flavoring compounds is simply not available.(6)

Finally, the last component is nicotine, with which the scientific community is all too familiar. In e-liquid it can be ordered in varying doses. However, the actual dosage delivered systemically is difficult to quantify for the average user as vaping styles vary considerably based on user experience with the devices. It is also important to consider that the purported nicotine doses are not rigorously accurate and have been shown to have wide ranges of error.(7)

Prevalence

Estimates of e-cigarette use in the literature primarily consist of user self reporting in the form of various surveys. Using these tools it is estimated that 1.8% of US adults had used one of these devices in 2010. As of 2013 that percentage rose to 13%.(4) Importantly, up to 20% of e-cigarette users were nonsmokers.(8)

Considerable focus has been on the trend of adolescent use. As mentioned earlier, use among high school students more than doubled from 2011 to 2012 (4.7% to 10%). An increase again up to 16% was noted for 2015. Leventhal et al have been following a cohort of students in Southern California longitudinally. While their data may not be directly applicable nationwide, it is nevertheless informative. Of primary concern in their studies is whether initiation of nonsmokers to electronic cigarettes leads eventually to traditional smoking of combustible cigarettes. They report a 30.7% use of combustible cigarettes at 6 month follow up for users of electronic cigarettes, (vs 8.1% in nonusers).(9) They similarly find that increasing the nicotine concentration in the vaping devices correlated with higher chances of initiating traditional smoking.(10)

A subsequent meta-analysis which included 9 studies and a total adolescent population of 17,389 found that prior e-cigarette use was associated with a 23.2% chance of smoking initiation (vs 7.2% in nonusers).(11) While these are observational studies and cannot determine causality, it seems plausible that a number of adolescents are initiating nicotine use with electronic cigarettes (having never smoked) and then progressing to traditional cigarettes or dual use.

Toxicity

Established long term data regarding the clinical effects of electronic cigarettes simply doesn't exist, given the devices' short history. Much of the medical literature to this point focuses on analyzing the chemistry of the e-liquid and the aerosol produced after heating, and determining if there are dangerous contaminants or carcinogens present. This is then often compared with the known quantities of these same substances in combustible cigarette fumes. It is interesting to note that the components are altered after exposure to extreme heat and potentially harmful chemicals are produced in the process. However, in most studies, the number of chemicals found as well as their concentrations are far lower than those found in combustible cigarettes. An exhaustive detailed review of these chemical analyses is beyond

the scope of this review. The overall findings are summarized well in the table below, adapted from reference (12):

Toxin	Conventional cigarette (μg/cigarette in mainstream smoke)	Electronic cigarette (μg per 15 puffs)	Average ratio (conventional: electronic)
Carbonyl compounds			
formaldehyde	1.6–52	0.20–5.61	9
acetaldehyde	52–140	0.11–1.36	450
acrolein	2.4–62	0.07–4.19	15
Toluene	8.3–70	0.02–0.63	120
Nitrosamines			
N′-nitrosonornicotine	0.005–0.19	0.00008–0.00043	380
NNK	0.012–0.11	0.00011–0.00283	40

Definition of abbreviation: NNK = 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone.

As can be seen in this summary, a handful of known carcinogens are found in low concentrations in the aerosol produced by electronic cigarettes. However, they are present in multiple orders of magnitude higher in combustible cigarettes. Additionally, over 7000 different chemicals have been found in cigarette smoke, while only a small handful of substances have been found present in e-cigarette aerosols. This data argues that, while the aerosol is not completely benign, it is likely to have far less adverse effects than combustible cigarettes. Longer term studies would obviously be needed to make a more definitive determination.

Peyton et al also report on the concentration of formaldehyde hemiacetal (a so called formaldehyde releasing agent).(13) This was produced in aerosols, only when very high voltage settings were used on vaporizers. (5V). None was detected a lower voltage (3.3V). If formaldehyde hemiacetal was considered equivalent to formaldehyde, the authors extrapolate that exposure from e-cigarettes could actually exceed combustible cigarettes, given typical daily use. While formaldehyde itself is a known carcinogen, the effects of formaldehyde releasing agents on the respiratory tract are not well defined. This observation, not only calls for additional study, but argues for better regulation and restriction of voltage ranges of these devices. In addition to the above, trace amounts of heavy metals can be found in e-cigarette vapor, speculated to represent contamination from the casing and heating elements.

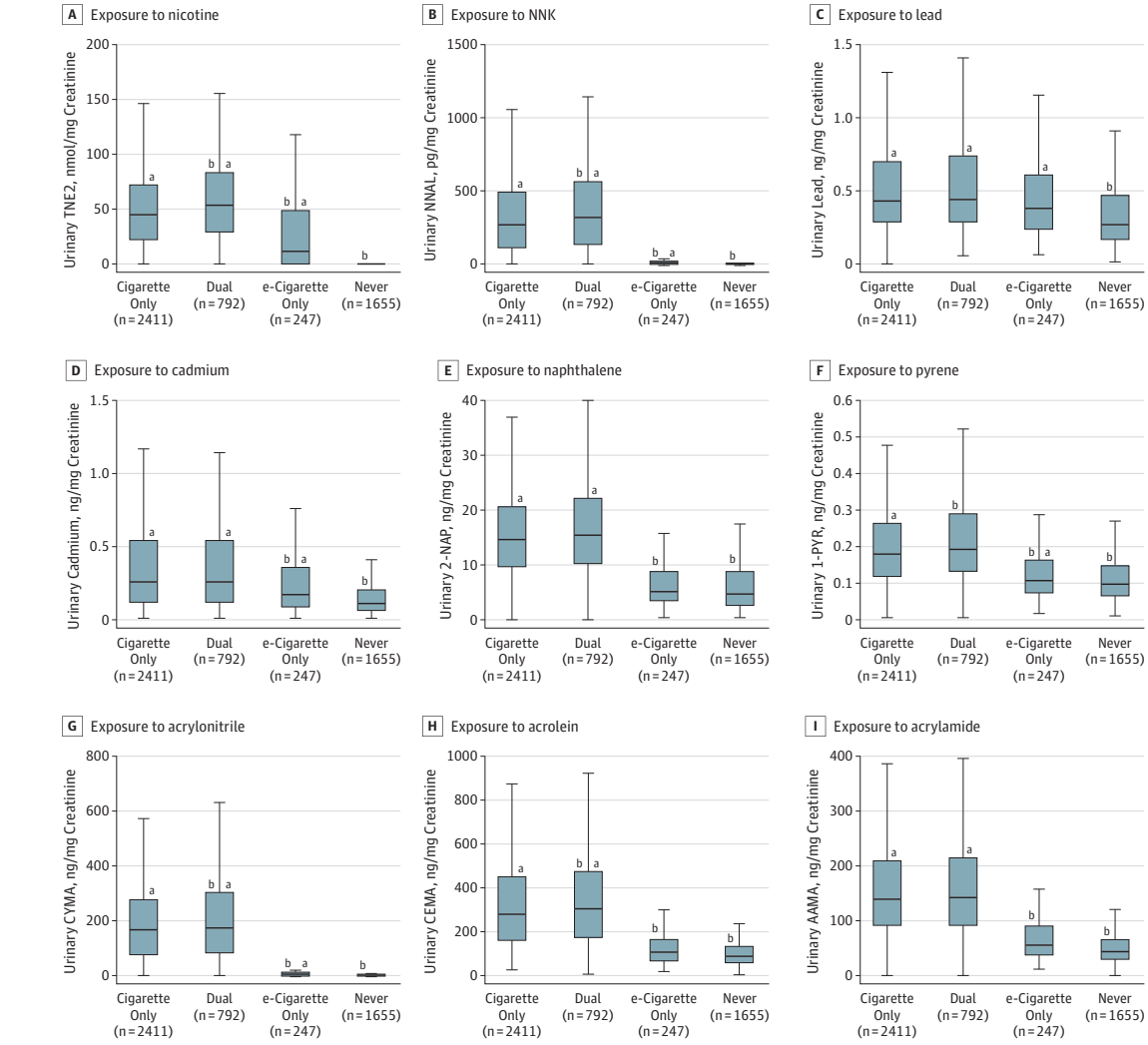
A study last month from JAMA dove further into this topic by examining the urine of over 5000 individuals for biomarkers of known tobacco product constituents. These were separated and analyzed as groups of smokers, nonsmokers, e-cigarette users, and dual users. They analyzed 50 different biomarkers in these samples. Representative and relevant markers are outlined in the chart below, with the associated known toxicity of these substances: (14)

Group	Chemical Exposure	Internal Biomarker	Clinical Relevance to Known or Suspected Diseases or Disorders
Urinary nicotine metabolites	Nicotine	TNE2[a]	Linked to impaired brain and lung development (fetal stage), altered development of cerebral cortex and hippocampus (adolescent stage), causal factor in nicotine dependence, addiction, and withdrawal disorders[33]
Tobacco-specific nitrosamines	4-(Methylnitros-amino)-1-(3-pyridyl)-1-butanone	4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanol	Known human carcinogen (International Agency for Research on Cancer Group 1)[39]
Metals	Lead	Urinary lead	Associated with brain damage, mental retardation, behavioral problems, developmental delays (fetal/youth/adolescent stage); linked to damage of sense organs and nerves, impaired cognitive function, as well as hearing and vision impairment in adults[37]
	Cadmium	Urinary cadmium	International Agency for Research on Cancer Group 1 known human carcinogen with adverse effects on kidney and bone; implicated in risk of diseases that involve tissues and organ systems where cadmium accumulates, including eye tissues[38]
Polycyclic aromatic hydrocarbons	Naphthalene	2-Napthol	International Agency for Research on Cancer group 2B possible human carcinogen; linked to respiratory tract lesions, including tumors in the upper respiratory tract demonstrated in animal studies, and respiratory irritation in humans[31]
	Pyrene	1-Hydroxypyrene	Accepted biomarker of carcinogenic polycyclic aromatic hydrocarbons; associated with lipid damage and alterations of endogenous and exogenous antioxidants; contributes to oxidative stress, associated with acute myocardial infarction[35]
Volatile organic compounds	Acrylonitrile	*N*-Acetyl-S-(2-cyanoethyl)-L-cysteine	International Agency for Research on Cancer group 2B carcinogen[32]
	Acrolein	*N*-Acetyl-S-(2-carboxyethyl)-L-cysteine	Vapor form may cause eye, nasal, and respiratory tract irritations in low-level exposure[34,42]
	Acrylamide	*N*-Acetyl-S-(2-carbamoylethyl)-L-cysteine	Probable contributor to cancer risk and an International Agency for Research on Cancer group 2A carcinogen[32]; acrylamide can be neurotoxic in humans and animals, causes peripheral neuropathies in workers who use or work in the manufacture of the product, and is a reproductive toxicant in mice[40]

Two interesting points about the individual groups are important in interpreting the results.

- 93% of the electronic cigarette group are former smokers (had quit an average of 3.5 years ago
- Combustible cigarette usage was similar in the smoking only vs dual user groups

Their findings for the above substances are illustrated in the graphs below:



For the majority of the substances tested, metabolites were found in significantly lower quantities in e-cigarette users than in combustible cigarette smokers, but still increased above levels found in never smokers. Dual users had the highest amount of metabolites measured across the board. But this makes sense, given that the dual users and cigarette only users smoked similar amounts of cigarettes, and the e-cigarette use was in addition to this.

The authors concede that the data is limited primarily to sampling during a time when only early generation electronic cigarettes were available. Newer models offer better efficiency of drug delivery and variable voltage settings, which may increase measurable toxicity. Additionally, it is unclear what role prior smoking may have played in these results, and samples of e-cigarette users without any prior smoking history would be interesting to compare. As discussed later, use of electronic cigarettes can be associated with a decrease in daily smoking, even if it does not lead to cessation. This type of "dual user" appears to be different from the population in this study as the authors note similar use of combustible cigarettes across the

smoking groups. It appears reasonable to speculate that substituting electronic cigarettes for combustible cigarettes (in full or in part) likely leads to decreased but not eliminated toxic exposure over time.

Pulmonary Function

Long term data regarding the effects on pulmonary function is obviously not available to this point. Small studies have shown no significant changes to spirometry after acute exposure to e-cigarette vapor, which is in contrast to changes seen with cigarette smoke. The clinical relevance of this is hard to determine.(15)

Wound Healing

An under studied aspect of electronic cigarettes is whether they can contribute to poor wound healing in the surgical population as combustible cigarettes certainly do. No definitive clinical studies are available to answer this question. However, Troian et al attempt to explore this issue using an animal model.(16) They exposed Sprague-Dawley rats to e-cigarette vapor vs traditional cigarette smoke vs control in a closed chamber for 30 minutes twice a day for 30 days (n=15 in each of the 3 groups). At the end of 30 days, skin flaps were surgically raised on all 45 rats, and subsequent percent of flap necrosis was measured. There was no statistically significant difference in necrosis among the rats exposed to smoke vs vapor. The control group had a significantly lower amount of necrosis. While this is far from definitive regarding human clinical outcomes, this study argues that the detrimental effects of smoking on surgical wound healing could be carried over to electronic cigarettes as well. It would be reasonable to counsel patients to stop completely prior to any major elective surgical procedures.

Alternative Toxicities

While comparison with traditional cigarettes is a reasonable avenue of inquiry, it is also important to consider whether there are any novel toxicities associated with electronic cigarettes. While this may be more clearly defined in time, a few examples are outlined below.

Lipoid Pneumonia

Viswam et al report a case of lipoid pneumonia attributed to electronic cigarette use in the British Medical Journal this year.(17) It is one of several similar case reports that can be found in the medical literature to date. Exogenous lipoid pneumonia has in recent years been primarily of historical significance. Essentially it consists of excessive lipid deposition in the lungs, overwhelming clearance by macrophages. It can present as radiographic infiltrates similar to community acquired pneumonia or can appear as discreet masses, often leading to

invasive procedures for diagnosis. In severe forms gas exchange can be affected and the patient can become symptomatic. It was previously associated primarily with oil based laxatives, which are no longer in use. It has occasionally also been described in niche occupations due to exposure (ie fire-eaters).

This case involved a 34 year old female who presented with 3 months of progressive shortness of breath, weight loss, and hemoptysis. She had been using electronic cigarettes for 3 years. Imaging demonstrated bilateral infiltrates and spirometry was significant for a restrictive physiology with a significantly impaired DLCO. BAL revealed lipid laden macrophages. She eventually underwent surgical lung biopsy demonstrating cholesterol clefts, consistent with a diagnosis of lipoid pneumonia. No other toxic exposures were able to be found. The diagnosis was attributed to the vegetable glycerin found commonly in e-liquid. She was treated with steroids, resulting in symptomatic improvement but her low DLCO remained.

ARDS:

Sommerfeld et al report a case of an 18 year old female who presented acutely with dyspnea and pleuritic pain that progressed rapidly to ARDS requiring mechanical ventilation.(18) This occurred after initiating electronic cigarettes just 2-3 weeks prior. The authors attributed this to acute hypersensitivity pneumonitis and she was initiated on systemic steroids with clinical recovery.

Other case reports have documented **acute eosinophilic pneumonia** associated with e-cigarette use.

It is impossible at this time to determine the relative danger of developing these conditions, or if there is any association with any particular brand of liquid or device. But it is important for the clinician to add these conditions to their differentials for infiltrates in users of electronic cigarettes.

Toxic Ingestion

Another issue to consider is the toxic oral ingestion of nicotine. E-liquid comes in containers that are often not child proof. Additionally they may have what appear to be child friendly labels (for example multiple colors with sweet sounding words like cotton candy). The taste may be sweet as well. However, the amount of nicotine present in an entire bottle may exceed a lethal dose, especially for a small child. All of this adds to a significant concern that toxic overdoses can occur. This is an area primarily unique to electronic cigarettes, as eating packs of traditional cigarettes is appealing to no one and less likely to occur.

Bassett et al report a toxic ingestion by a 10 month old infant.(19) The child presented with vomiting, tachycardia, grunting respirations, and truncal ataxia. This child recovered, but higher doses can lead to neuromuscular blockade, respiratory failure, and death.

Indeed increased calls to poison centers for nicotine ingestion has been documented over the last several years.(20) And there has been at least one case of an adult suicide accomplished by drinking e-liquid.

Regulation of labels and containers would go a long way toward curtailing this issue. But public education regarding the toxicity of these substances when ingested in large quantities is important as well. If there is a lack of understanding about this danger, then typical safeguards are easily overlooked by individual users.

Smoking Cessation

Although there appears to be at least some toxicity associated with electronic cigarettes, this could be negated if they prove to be highly effective tools in smoking cessation. Compared with other products such as nicotine patches, gum, and pharmaceutical methods, e-cigarettes most closely mimic the actual experience of smoking. For many smokers, the habit and ritual of smoking is difficult to give up, over and above the addictive effects of nicotine. If these newer products could alleviate this difficult aspect of cessation then they could be extremely worthwhile from a medical standpoint. To date these benefits have not yet been fully realized.

A study published in Lancet randomized 657 people that wanted to quit cigarettes to the use of electronic cigarettes, nicotine patches, and placebo (e-cigarettes without nicotine). The primary endpoint was abstinence at 6 months.(21) There was a higher rate of abstinence at 6 months in the e-cigarette group (7.3% vs 5.8% with patches). However, the result was not statistically significant. There was a significant difference in favor of electronic cigarettes at 1 month but this did not carry out through the rest of the study. The authors had powered the study for an estimated 20% rate of abstinence and the low overall success across all groups may have led to the negative result. They also note that there was a higher dropout rate in the group assigned to patches. No adverse events were noted across any of the groups. Overall this argues that electronic cigarettes are perhaps at least noninferior to patches for smoking cessation. Further studies to better define cessation protocols with electronic cigarettes may be able to increase their effectiveness.

Another study relying on survey results demonstrated a 31% quit rate in electronic cigarette users.(22) While this compares favorably to abstinence rates documented elsewhere using more traditional methods, it is difficult to generalize these results or compare them directly to other studies. However, the authors also note that a very large percentage (66.8%) of electronic cigarette users reported at least a reduction in smoking even if abstinence was not achieved.

Harm Reduction vs Renormalization

The debate regarding the future of electronic cigarettes centers around these 2 broad concepts. The above data illustrates that these products are likely to be less harmful than combustible cigarettes but are not completely benign either. Proponents of a harm reduction strategy argue that use of e-cigarettes could encourage less traditional smoking and perhaps even its elimination, leading to considerably less tobacco induced disease burden.(23) This is theoretically plausible, but as seen above, there is not data to this point which supports this strategy. E-cigarettes have not yet been shown to support cessation better than other established (and perhaps less toxic) methods. Their initiation has also been seen to lead to dual usage, which can carry with it an overall increase in carcinogen exposure. For many smokers, it becomes easy to continue smoking and just use e-cigarettes in places where traditional smoking is inconvenient or disallowed.

This leads to the renormalization argument.(24) It is felt that the general decline in smoking over the last few decades has a lot to do with it becoming less and less accepted in general society. As the public has overall become more educated regarding the dangers, and as it has been restricted or forbidden in so many public places, it is simply encountered far less than in prior years. As an example, restaurants and bars have virtually eliminated indoor smoking in many major cities. There is great concern that e-cigarettes could emerge as a popular, safe, and "accepted" form of nicotine delivery and could bring these types of products back to the forefront of society, perhaps leading again to an increase in overall nicotine addiction. In a worst case scenario, this could eventually lead to an increase in smoking as well. Proponents of this argument point to studies where e-cigarette use appears to correlate with later smoking, especially in adolescents. They also express concern regarding the propensity for e-cigarettes to attract never smokers, likely due to perceived safety of the devices.

The medical community in general harbors a general mistrust of major tobacco companies based on past practices regarding marketing and disclosure of safety. Some have drawn comparisons to the days when filters were added to cigarettes, which were then marketed as "safe". It seems important to note that all of the major tobacco companies have heavily invested in e-cigarettes. There may be a public perception that these devices and liquids are made and sold by "independent" shops, but many are actually owned by the major cigarette corporations. They may see this as their monetary future as sales on cigarettes dwindle. When there is considerable motivation for profit, there is reason for concern about whether rigorous pursuit of truth regarding safety and public health is being taken seriously.

Conclusions and Advice for Patients:

- It is difficult to give definitive recommendations one way or the other due to lack of long term safety data
- Base on the available information, electronic cigarettes appear to be safer when compared to combustible cigarettes, but are not benign

- Electronic cigarettes remain addictive when containing nicotine and may lead to progression to smoking
- It is possible that they may be an effective tool in smoking cessation, but that has not been reliably shown. The best data shows them to be equivalent to nicotine patches in efficacy, with potentially increased toxicity.
- Marketing to youth, as well as public perception of safety, may lead to initiation of electronic cigarettes by nonsmokers, leading to an overall increase in nicotine addiction

References:

1. Collaco JM, Drummond, MB, McGrath-Morrow SA. Electronic Cigarette Use and Exposure in the Pediatric Population. JAMA Pediatrics 2015 169(2) 177-182.
2. Arrazola RA, Singh T, Corey CG, et al. Tobacco Use Among Middle and High School Students-United States. 2011-2014. MMWR 2015 64(14) 381-385.
3. Chang AY, Barry M. The Global Health Implications of e-Cigarettes. JAMA 2015 314(7) 663-664.
4. Dinakar C, O'Connor GT. The Health Effects of Electronic Cigarettes. N Engl J Med 2016 375(14) 1372-1381.
5. Callahan-Lyon P. Electronic Cigarettes: Human Health Effects. Tob Control 2014 23:ii36-ii40
6. Barrington JL, Samet JM, McConnell R. Flavorings in Electronic Cigarettes: An Unrecognized Respiratory Health Hazard? JAMA 2014 312(23) 2493-2494.
7. Schraufnagel DE, Blasi F, Drummond MB, et al. Electronic Cigarettes: A Positioin Statement of the Forum of International Respiratory Societies. Am J Respir Crit Care Med 2014 190(6) 611-618.
8. McMillen RC, Gottlieb MA, Winickoff JP. E-Cigarettes: The Roles of Regulation and Clinicians. JAMA Internal Medicine 2015 175(10) 1603-1604.
9. Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence. JAMA 2015 314(7) 700-707.
10. Goldenson NI, Leventhal AM, Stone MD, et al. Associations of Electronic Cigarette Nicotine Concentration With Subsequent Cigarette Smoking and Vaping Levels in Adolescents. JAMA Pediatrics 2017 171(12) 1192-1199.
11. Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, et al. Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. JAMA Pediatrics 2017 171(8) 788-797.
12. Drummond MB, Upson D. Electronic Cigarettes Potential Harms and Benefits. AnnalsATS 2014 11(2) 236-242.
13. Jensen RP, Luo W, Pankow JF, et al. Hidden Formaldehyde in E-Cigarette Aerosols. N Engl J Med 2015 372(4) 392-394.
14. Goniewics ML, Smith DM, Edwards EC, Blount BC, et al. Comparison of Nicotine and Toxicant Exposure in Users of Electronic Cigarettes and Combustible Cigarettes. JAMA Network Open 2018 1(8) e185937
15. Palazzolo DL. Electronic Cigarettes and vapin: an new challenge in clinical medicine and public health. A literature review. Frontiers in Public Health. 2013 1 (56) 1-20.
16. Troiano C, Jaleeel Z, Spiegel JH. Association of Electronic Cigarette Vaping and Cigarette Smoking With Decreased Random Flap Viability in Rats. JAMA Facial Plast Surg 2018 doi.10.1001/jamafacial.2018.1179
17. Viswam D, Trotter S, Burge PS, Walters GI. Respiratory failure caused by lipoid pneumonia from vaping e-cigarettes. BMJ Case Rep 2018. doi:10.1136/bcr-2018-224350.
18. Sommerfeld CG, Weiner DJ, Nowalk A, Larkin A. Hypersensitivity Pneumonitis and Acute Respiratory Distress Syndrome From E-Cigarette Use. Pediatrics 2018 141(6) e20163927
19. Bassett RA, Osterhoudt K, Brabazon T. Nicotine Poisoning in an Infant. N Engl J Med 2014 370(23) 2249-2250.
20. Cantrell FL. Adverse Effects of e-Cigarette Exposures. J Community Health 2014 (39) 614-616.

21. Bullen C, Howe C, Laugesen M, et al. Electronic cigarettes for smoking cessation: a randomized controlled trial. The Lancet 2013 (382) 1629-1637.
22. Siegel MB, Tanwar KL, Wood KS. Electronic Cigarettes As a Smoking-Cessation Tool. Am J Prev Med 2011 40(4) 472-475.
23. Fairchild AL, Lee JS, Bayer R, Curran J. E-Cigarettes and the Harm-Reduction Continuum. N Engl J Med 2018 378(3) 216-219.
24. Fairchild AL, Bayer R, Colgrove J. The Renormalization of Smoking? E-Cigarettes and the Tobacco "Endgame". N Engl J Med 2014 370(4) 293-295.