Review Article

Efficacy and Safety of Electronic Cigarettes for Smoking Cessation: A Critical Approach

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Cigarette smoking accounts for more deaths and diseases worldwide than any other modifiable risk factor. Indeed, smokers have a two- to fourfold increased risk for developing coronary artery disease and stroke.[1-3] There is also a 25-fold increased risk of lung cancer.[4] In addition, numerous respiratory illnesses, congenital malformations, immune dysfunctions and other co-morbidities are seen more frequently in smokers than non-smokers.[5]

Quitting smoking is extremely difficult for most smokers, since nicotine is highly addictive and cessation is associated with withdrawal symptoms. To cope with withdrawal symptoms and to obtain relief, both psychosocial counseling and pharmacotherapy are effective methods, but they are most effective when used together. The first-line pharmacological substances licensed to aid smoking cessation are nicotine replacement therapy, bupropion and varenicline. All these medications are considered effective and appropriate smoking cessation strategies.[1,6]

Electronic cigarettes (e-cigarettes) have the potential of targeting the access of nicotine to the brain and thereby to prevent the nicotine reinforcing effects.[7,8] Proponents of e-cigarettes insist that e-cigarettes are healthier than traditional tobacco products and are an effective smoking cessation tool. Their supporters argue that some electronic nicotine delivery systems show considerable promise in the fight against tobacco-related morbidity and mortality. Others, however, express concerns related to the lack of knowledge regarding the long-term effects of e-cigarette use, the evidence of toxic chemical content, the increasing e-cigarette use rates among young people, and, finally, the lack of government regulation, consumer protection requirements, and product quality standards.

Considering the frequent use of e-cigarette smoking together with concerns for public health, the aim of this review article is to highlight the efficacy for smoking cessation and the potential hazards of e-cigarette smoking.

Methods

For this systematic review we searched the PubMed electronic database until June 2015 using as main keyword the term "electronic cigarette", as well as related keywords (e-cigarette, electronic nicotine delivery systems). We retrieved a total of 114 publications relevant to research on e-cigarette safety/risk profile. The validity and strength of each study were determined based on a qualitative assessment of study objectives, methods and population. In total, 20 original papers and 8 review articles and statements relevant to

research on e-cigarette safety/risk profile are cited in this review article.

What is the e-cigarette?

The electronic nicotine delivery systems incorporated in e-cigarettes are devices in which liquid nicotine is heated by a battery, transformed into an aerosol (often called "vapor"), and inhaled by the user.[7,9] Unlike traditional cigarettes or other combustible tobacco products, e-cigarettes do not contain tobacco, and because nothing is burned they emit no smoke. It is estimated that the e-cigarette devices and liquid used deliver one third to one fourth the amount of nicotine of smoking one standard cigarette after 5 minutes of use (Figure 1).[10] New-generation e-cigarette devices are more efficient in nicotine delivery but still deliver nicotine much more slowly than tobacco cigarettes. It should be noted, however, that e-cigarette users do not "smoke" in 5-minute sessions (as with a regular cigarette) but may do so over an extended period of time, thus potentially absorbing large amounts of nicotine.

Since their initial manufacture in 2003, there has been rapid growth and evolution in the types, design, and overall engineering characteristics of e-cigarettes. This has resulted in a large degree of product variability in size, potential nicotine concentrations, and e-liquid formulations. There have also been changes in the electrical circuitry (e.g. heating element or atomizer) and battery life that allow for more liquid delivery, adjustments in flavor, and longer device use. Ongoing product development and evolution are likely to continue; therefore, regulatory policies will be important to ensure appropriate quality control.[7-9,11]

E-cigarettes among young individuals

The use of e-cigarettes among young people is growing. The number of high school students who never used tobacco but had tried e-cigarettes tripled between 2011 and 2013. Some argue that this percentage is higher if non-cigarette nicotine delivery devices, such as electronic hookahs or "vape pipes", are included in the count.[5]

There is also concern among public health advocates that e-cigarettes could increase nicotine addiction and serve as a gateway to the use of tobacco products, particularly among the young. Indeed, although this is debated in the literature, evidence sug-

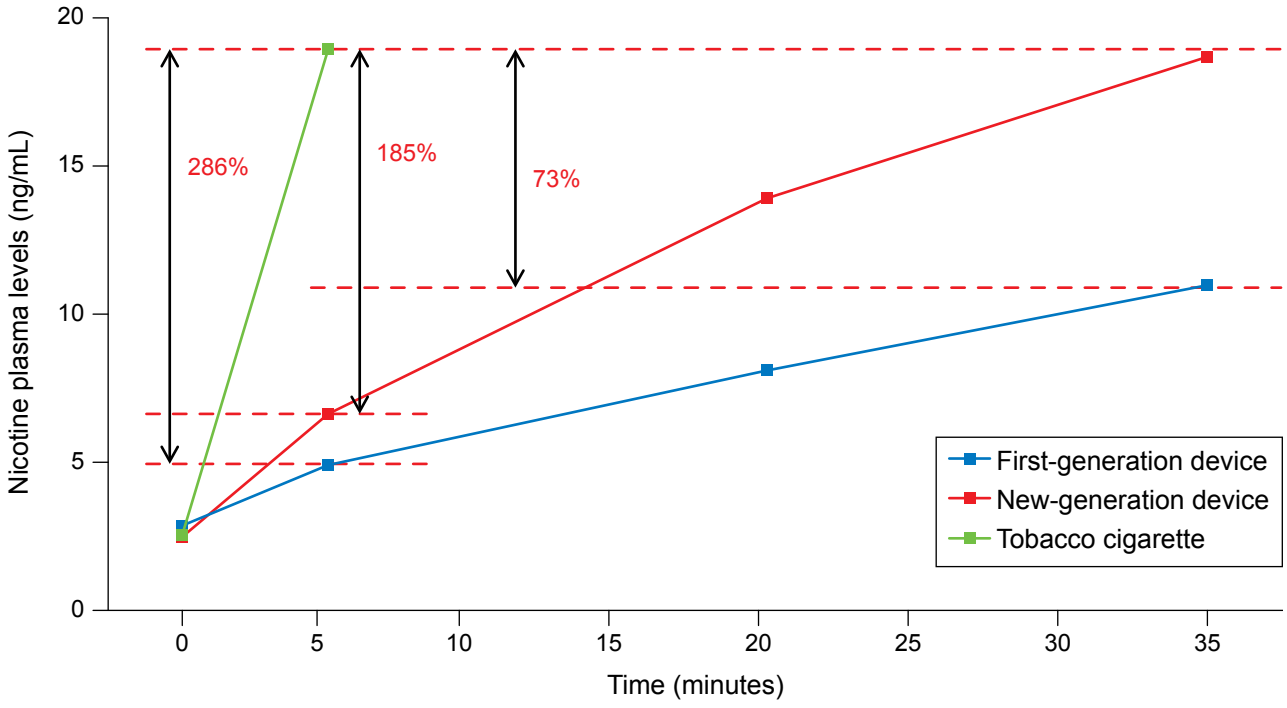

Figure 1. Comparison between tobacco cigarette and e-cigarette devices regarding nicotine levels. After 5 minutes of e-cigarette use, plasma nicotine levels were substantially lower compared to smoking one tobacco cigarette (almost 3-fold lower for new- and 4-fold lower for first-generation devices). Plasma nicotine levels are equal between tobacco cigarette use at 5 minutes and new generation e-cigarette device at 35 minutes. (Data from Farsalinos et al[10] with permission.)

gests that the intention to smoke traditional cigarettes is twice as prevalent in young persons who had tried e-cigarettes versus nonusers.[12] In addition, the 2011-2013 National Youth Tobacco Survey found that, among young people who smoked combustible cigarettes, 20% reported that they also had tried e-cigarettes.[13]

Potential for smoking cessation (Table 1)

The use of e-cigarettes for the management of tobacco dependence is controversial, because of the paucity of long-term safety results and randomized, controlled data.[14,15] Some argue that e-cigarettes have potential as smoking cessation aids and that the devices deliver nicotine to the user without many of the harmful constituents found in traditional tobacco smoke. An additional advantage, say proponents, is that e-cigarettes mimic the tactile and sensory experience of smoking, giving the quitting process a stepwise, and thus more easy to adopt, nature. One particularly large survey reported 81% complete smoking substitution with a median time of e-cigarette use of 10 months.[16] Furthermore, a longitudinal study of e-cigarette use reported that daily users of e-cigarettes were 6 times as likely as nonusers/triers to report quitting.[17] The results of EffiCiency and safety of an eLectronic cigAreTte (ECLAT), the first prospective 12-month randomized controlled trial, suggest that e-cigarettes help combustible tobacco smokers reduce or abstain from use.[18] In view of the fact that subjects in this study had no immediate intention of quitting, the reported overall abstinence rate of 8.7% at 52 weeks was remarkable.[18] A study by Polosa et al, found a sustained 50% reduction in the number of cigs/day in 32.5% of smokers who participated in a 24-week study. Notably, these participants did not originally intend to quit smoking.[19]

However, others conclude that the potential of e-cigarettes to help smokers quit is not clear.[20-22] Bullen et al, compared smoking abstinence rates at 6 months for those who used e-cigarettes, nicotine patches, and placebo e-cigarettes (nicotine-free).[23] Verified abstinence rates at 6 months were 7.3% for nicotine e-cigarette users, 5.8% for nicotine patch users, and 4.1% for placebo e-cigarette users. This study did not demonstrate any superiority of nicotine e-cigarettes compared to the other treatments.[23] It is also impossible to comment on the efficacy of e-cigarettes versus other interventions, such as varenicline or bupropion for cessation, given the lack of comparator groups in the studies.[24] The World Health Organization's 2014 report on e-cigarettes found "insufficient evidence" to support e-cigarettes as a smoking cessation aid and reiterated its recommendation that existing approved cessation aids be used.[25] A policy statement from the American Heart Association notes that "current evidence suggests a modest effect on cessation at best, likely equal to or slightly better than nicotine patches without behavioral support", and maintains that further research and regulation is urgently needed.[13]

Are e-cigarettes safe?

Effect on pulmonary function

Although e-cigarettes do not contain as many toxic substances as those in cigarette smoke, a recent FDA review reported that various chemical substances and ultrafine particles known to be toxic, carcinogenic, and/or responsible for the causation of respiratory and heart distress have been identified in e-cigarette aerosols, cartridges, refill liquids, and environmental emissions.[4,11] Indeed, the e-cigarette aerosol can cause upper respiratory tract irritation, dry cough, dryness of the mucous membrane, release of cytokines and pro-inflammatory mediators, allergic airway inflammation, decreased exhaled nitric oxide (FeNO) synthesis in the lungs, changes in bronchial gene expression, and a risk of lung cancer (Table 2).[24] However, further research is needed to determine the long-term effects of inhalation of e-cigarette aerosol on lung function.[26]

Table 1. Efficacy of nicotine vs. non-nicotine e-cigarettes for smoking cessation.

	Number of studies	OR	95% CI
Abstinence from tobacco smoking	2	2.29	1.05-4.96
Reduce cigarette smoking by at least half (vs. placebo)	2	1.31	1.02-2.68
Reduce cigarette smoking by at least half (vs. NRT)	1	1.41	1.20-1.67

Data are derived from McRobbie et al 2014[14] and Rahman et al 2015.[15]
OR – odds ratio; CI – confidence interval; NRT – nicotine replacement therapy.

Table 2. Effect of e-cigarette smoking on parameters of cardiovascular and pulmonary function. (Modified from Orellana-Barrios et al[9] with permission.)

	Effect
Cardiovascular parameters:	
Systolic and diastolic BP	Significant diastolic BP increase,
Heart rate	Increase after 5 min, lower than traditional cigs
Systolic and diastolic cardiac function	No effect
Vascular function	PWV increase, but smaller than traditional cigs, preliminary data
Pulmonary function parameters:	
Carbon oxide	No impact
Oxygen saturation	No definite effect with contradicting studies
Exhaled NO	Immediate decrease
Airway resistance	Significant (18%) increase
Respiratory impedances	Significant increase, including nicotine-free solutions

BP – blood pressure; PWV – pulse wave velocity NO – nitric oxide.

Cardiovascular effects

Few studies have reported the immediate effect of e-cigarette use on cardiovascular parameters (Table 2).[27] Mild e-cigarette liquid inhalation is associated with tachycardia, chest pain and high blood pressure.[27,28] More serious events reported are bradycardia, hypotension, respiratory paralysis, atrial fibrillation and dyspnea.[27,28] E-cigarettes increase systolic and diastolic blood pressure as well as heart rate, but in general, most studies show a smaller magnitude of increase compared to traditional cigarette smoking.[29] Furthermore, although smoking acutely causes a delay in myocardial relaxation, e-cigarette use has no such immediate effect.[30]

Although smokeless tobacco-related cardiac events have been studied in the past, it is difficult to extrapolate data to e-cigarettes, considering their different mechanism of nicotine delivery.[31] There are also currently no published studies on e-cigarette use and thrombosis, platelet reactivity and atherosclerosis.[32-36] Preliminary data from our department show that e-cigarettes increase aortic stiffness.

Nicotine and other chemical substances

Nicotine, which is a highly addictive compound, is delivered by most, but not all e-cigarette products.[8] Nicotine may promote tumor growth, compromise treatment success, and negatively affect the neurological development of adolescents.[11,24,37] Propylene glycol and glycerin are the most common nicotine solvents used in e-cigarettes.[38] Propylene glycol can irritate the eye and respiratory system. Heavy metals, such as tin, lead, and nickel, have also been discovered in a brand of e-cigarette nicotine liquids and aerosols.[39] These metals can negatively affect the nervous and respiratory systems.

Importantly, e-cigarette aerosol contains toxic chemicals, such as formaldehyde and acetaldehyde, at rates 9 to 450 times lower than those of combustible cigarettes and comparable to amounts contained in a nicotine inhaler.[38,39] Both solvent and battery output voltage significantly affect levels of carbonyl compounds in e-cigarette vapors. New generation high-voltage e-cigarettes may put their users at increased health risk from exposure to high levels of carbonyl compounds, although the risk will still probably be much lower compared with smoking.[40]

Conclusions

Electronic cigarettes are growing in popularity, but their safety and efficacy as a smoking cessation aid are not well explored. Some argue that they have the potential to reduce tobacco-related morbidity and mortality and could be a useful tool for reducing tobacco-related harm. Others express concern that the health effects of e-cigarette use are unknown, that they may appeal to young people, and that they may encourage dual use of e-cigarettes and traditional tobacco products. E-cigarette use as a tobacco cessation product is not currently approved by any regu-

latory body, and a recent FDA-proposed regulation signals a possibly harsher FDA position toward the e-cigarette industry. Both the World Health Organization (WHO) and the American Heart Association (AHA) reports voiced fears that, rather than help get rid of tobacco once and for all, e-cigarettes could make smoking culturally acceptable once again. The AHA also issued its policy statement on e-cigarettes, saying that the devices should be regulated like tobacco products by state and local governments, including them in smoke-free laws and taxing them to discourage use by teenagers. The majority of the studies performed with the aim of assessing the cardiovascular effects of e-cigarettes are focused on the acute effects on the heart. Further research is needed to examine the longer-term safety, potential for long-term use and efficacy as a cessation aid. Finally, it cannot be overemphasized that it is important to advise all smokers to quit smoking traditional cigarettes, encourage the use of cessation medications approved by regulatory bodies, and refer patients for smoking cessation counseling.

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