Addiction

REVIEW

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Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit

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ABSTRACT

Aims We reviewed available research on the use, content and safety of electronic cigarettes (EC), and on their effects on users, to assess their potential for harm or benefit and to extract evidence that can guide future policy. **Methods** Studies were identified by systematic database searches and screening references to February 2014. **Results** EC aerosol can contain some of the toxicants present in tobacco smoke, but at levels which are much lower. Long-term health effects of EC use are unknown but compared with cigarettes, EC are likely to be much less, if at all, harmful to users or bystanders. EC are increasingly popular among smokers, but to date there is no evidence of regular use by never-smokers or by non-smoking children. EC enable some users to reduce or quit smoking. **Conclusions** Allowing EC to compete with cigarettes in the market-place might decrease smoking-related morbidity and mortality. Regulating EC as strictly as cigarettes, or even more strictly as some regulators propose, is not warranted on current evidence. Health professionals may consider advising smokers unable or unwilling to quit through other routes to switch to EC as a safer alternative to smoking and a possible pathway to complete cessation of nicotine use.

Keywords Electronic cigarettes, harm reduction, prevalence, product safety, regulation, smoking cessation.

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INTRODUCTION

Electronic cigarettes (EC) are devices designed to deliver nicotine without tobacco smoke by heating a solution of nicotine, flavouring, additives and propylene glycol and/or vegetable glycerine. Invented by Lik Hon in Hong Kong in 2003 [1], they became available in Europe and the United States in 2006 [2]. EC are undergoing a rapid evolution driven by competition. There are dozens of manufacturers and hundreds of EC models. Tobacco manufacturers joined this market in 2012, when Lorillard bought Blu e-cigs (http://investors.lorillard.com/investor-relations/news/2012/default.aspx).

During the past few years EC have been gaining popularity, primarily among smokers who want to reduce the risks of smoking [3,4]. The growing sales of EC, driven initially by word of mouth and user enthusiasm, are now seen by financial analysts to threaten sales of cigarettes [5,6]. The reaction by the public health community to this unfolding phenomenon has ranged from enthusiastic support to vigorous opposition. Regulatory bodies around the world are deciding whether to allow EC to compete with cigarettes freely, submit them to a more restrictive regulation than cigarettes, e.g. as medicinal devices, or ban them. Their verdicts will probably feature among the key public health decisions of our time.

Commentators in favour of EC restrictions believe that the product has a potential to increase cigarette use by re-normalizing smoking, i.e. reducing motivation of smokers to quit completely, providing a gateway to smoking for non-smokers or facilitating an increase in smoking prevalence indirectly. They argue that EC should be banned or submitted to much stricter controls than smoked tobacco. They emphasize evidence that nicotine can be addictive and warn that health risks from long-term EC use may yet emerge (e.g. [7–10]).

EC advocates believe that, on the contrary, the product has a potential to reduce and, if it continues to develop, eventually end cigarette use by allowing smokers to switch to a safer product. They argue that achieving this potential requires little government expenditure and involvement and that it is in the public health interest to allow EC to compete with cigarettes in the market-place. They emphasize evidence that use of nicotine without tobacco toxicants poses minimal risks, except in the case of well-defined subpopulations such as pregnant smokers (e.g. [11–15]).

Both sides of the debate agree that any policy and regulatory decisions affecting EC should be guided by evidence. This review summarizes the literature on patterns of EC use, content, safety and effects on users and considers the implications of the evidence.

Search strategy and selection criteria

We searched Medline, PsycINFO, EBM reviews (including Cochrane Methodology Register, Health Technology Assessment and NHS economic evaluation database), Google Scholar, EMBASE and CINAHL (to February 2014). We combined the following search terms 'e-cig*' OR 'elect* cigar*' OR 'electronic nicotine'. We also searched the reference lists of articles identified by this search strategy and selected those that addressed the key themes of the review. After removing duplicates, this search identified 286 records that were screened independently by two reviewers (P.H. and H.M.). Most papers were opinion-pieces. Ninety-nine full-text papers were reviewed. Papers were deemed relevant ($n = 81$) to this review if they presented original data and provided evidence that could guide regulatory decisions.

Note that we use the words 'EC' for electronic cigarettes and 'cigarettes' for conventional cigarettes. EC use is increasingly labelled as 'vaping' and EC users as 'vapers', but we are using EC use/EC user throughout.

SURVEYS OF EC USERS

Prevalence of EC use and characteristics of users

EC use was negligible in 2008–09, but increased steadily over the following years: in the United States in the general population it increased from 0.6% in 2009 to 2.7% in 2010 [16] and to 6.2% in 2011 [17]. In the United Kingdom, use in smokers increased from 2.7% in 2010 to 6.7% in 2012 [2] and to 11% in 2013 [18]. About one-third (30% to 38%) of ever users used EC within the past 30 days [2,16,17,19–23]. Some 12–14% of smokers who tried EC progressed to daily use [23,24].

EC users tend to be younger, more educated and have higher income than non-users [17,25,26]. There is no clear association between e-cigarette use and gender [20,26–28]. Most of these surveys are from Europe and the United States, and the results may not apply to other countries.

EC experimentation and regular use by never-smokers

Studies conducted to date have found that the prevalence of EC experimentation (ever use) in never-smokers ranged from 0.1 to 3.8% (median 0.5%), and use in the past 30 days ranged from 0 to 2.2% (median 0.3%) [2,16,17,20,22,23,25,27–29]. A recent report on EC use among US children was interpreted as showing worryingly high levels of use [30], but extrapolated data show that among middle school students in 2012, 0.5% of never smokers tried EC. The figure for high school students was 0.7%. Among children, current use was confined to those who have already tried smoking [18]. 'Current use' in non-smokers (any use over the past 30 days, not daily use) was reported in only 0.04% [31]. A study assessing daily use in non-smokers found none [23]. For comparison, 39.5% of twelfth-graders (17–18-year-olds) tried cigarettes in the United States in 2011 [32], and about half of children who try conventional cigarettes progress to regular use.

Surveys of regular EC users

A number of studies recruited EC users over the internet. These results need to be interpreted with caution, because internet surveys attract primarily EC enthusiasts [3].

The most popular e-liquids had a nicotine content of 18 mg/ml [3,33–37], and the most popular flavours were tobacco, mint and fruit [3,4,36,38].

Users reported consistently that EC helped them either to quit smoking (42–99%) [3,4,34–37,39] or to reduce it (60–86%) [3,24,36,39]. EC were perceived as less addictive than cigarettes [35,37], and time from waking up to use was longer for EC than for cigarettes [36,37]. Only 18% reported that they craved EC as much as tobacco [36].

Summary

EC use is on the increase. Experimentation by children is a small fraction of experimentation with cigarettes, and daily use in never-smokers has not been documented so far. It appears that some 12–14% of smokers who try EC become daily users, suggesting that EC in their current form are less satisfactory than cigarettes to most users. In surveys, regular EC users report that these devices helped them to limit or stop smoking and they perceive EC as less addictive than cigarettes.

EC CONTENT

The interpretation of studies of the chemical composition of the e-liquids and aerosols is complicated by the fact that there exist many brands and models with different e-liquids, batteries, heating elements, nicotine concentrations and flavourings, although most of them use e-liquids from a small number of manufacturers in China, the United States and Europe [40]. It is also important to differentiate between the chemical compositions of e-liquid and aerosols that users inhale.

Propylene glycol (PG) and glycerol

The results of extensive studies on animals, reviewed elsewhere [40,41], suggest that PG should be safe for inhalation in humans, although in children, chronic exposure to PG in indoor air may exacerbate or induce rhinitis, asthma, eczema and allergic symptoms [42]. Acute and chronic respiratory effects, including reduced lung function, were reported in people chronically exposed to theatre fogs containing PG [43]. PG has a desiccation effect, which is why EC users sometimes report dry throat and mouth [3,4,36,37].

Glycerol (purified vegetable glycerine) is non-toxic, but can produce toxic acrolein when heated to higher temperatures. Acrolein was detected in the aerosol of some EC brands, but at levels much lower than in cigarette smoke [44]. Acrolein intake by smokers given glycerol-based EC was reduced by 60% in those who continued to smoke (EC use was accompanied by a reduction in smoking) and by 80% in those who stopped smoking [45].

Impurities and toxicants in e-liquids

Nicotine in e-liquids, like nicotine in nicotine replacement treatment (NRT), is extracted from tobacco and thus includes impurities such as cotinine, anabasine, anatabine, myosmine and beta-nicotyrine [46,47]. An early study found nitrosamines and tobacco-specific impurities 'at very low levels' and diethylene glycol in one of the cartridges [48]. Later studies of other products found no evidence of diethylene glycol [46]. No tobacco-specific nitrosamines or polycyclic aromatic hydrocarbons were found in 20 EC products [49], while an analysis of samples from 11 manufacturers [50] found nitrosamine concentrations approximately 1000 times lower than those in smokeless tobacco products [51]. Analysis of EC aerosol (as opposed to e-liquid) identified low levels of some toxicants [44]. In some cases these were comparable to levels found in NRT, which are considered safe, and overall at levels 9–450 times lower than in cigarette smoke [44].

Metal particles were found in the liquid and aerosol from an EC model [52], but the report did not assess the clinical significance of the levels detected. These levels are 10–50 times below the levels allowed in inhalation medicines [53].

EC liquid can be cytotoxic in *in-vitro* studies (e.g. [54]) but users inhale aerosol, not liquid. Aerosol from one of 21 e-liquids was cytotoxic, due to the flavouring containing substances from roasted coffee beans, but this was 800 times less cytotoxic than tobacco smoke [55].

PG and glycerol inhalation is likely to pose a low risk, although their long-term effects as well as the effects of long-term inhalation of EC flavourings and additives need to be studied.

Passive exposure

Most second-hand smoke from cigarettes is generated as sidestream smoke from the tip. EC do not generate sidestream aerosol. It is only what is exhaled by the users that enters the ambient air. EC aerosol does not include most of the chemicals found in tobacco smoke or the 'sidestream' smoke, but users exhale nicotine and some other particles, primarily consisting of flavours, aroma transporters, glycerol and PG [56–59].

No long-term study has been conducted so far, but pollutant levels are much lower than from cigarettes and are likely to pose a much lower risk (if any) compared to cigarettes [41,56].

Labelling of nicotine content of e-liquid

Nicotine is the addictive chemical in tobacco smoke, but its involvement in smoking-related harm (outside pregnancy) is very small, if any, compared to cigarette smoking [60,61].

In several reports, nicotine was detected in products labelled as zero nicotine. In one study, a manufacturer included similar nicotine levels in differently labelled cartridges, including zero nicotine [47]. In all other cases, nicotine detected in zero-nicotine cartridges was only at trace levels and unlikely to have any psychoactive effects [47–49].

For the major e-liquid brands tested thus far, the labelling of nicotine content is accurate [46] and the nicotine content across cartridges and across batches has good consistency [62,63], although labelling for some brands can be vague, inaccurate or absent. However, beyond the general rule that EC users cannot obtain high nicotine levels if there is too little nicotine in the e-liquid, there is little relationship between nicotine in cartridges and nicotine in aerosol [63]. This is because the mechanical features of EC, such as the size of the battery, the nature of the heating element and the ventilation holes, etc. play a major role. In addition, individual inhalation characteristics have further substantial influence on nicotine levels delivered to the user (see below).

Summary

E-liquids and aerosols tested so far contain some toxicants in concentrations much lower than in tobacco smoke and negligible concentrations of carcinogens. Passive exposure to EC aerosol can expose non-users to nicotine, but at concentrations unlikely to have any pharmacological significance. Humectants in EC appear to be safe for inhalation, but the effects on EC users with asthma and other respiratory diseases are not known. Nicotine intake from EC is determined by a host of factors in addition to nicotine content of the e-liquid.

EC SAFETY

Adverse events

None of the experimental [37,59,64–73] or prospective follow-up studies [74,75] reported serious adverse events (SAEs). Adverse events (AEs) were mild to moderate and included symptoms such as mouth and throat irritation and dry cough, similar to those reported in surveys of EC users [3,4,35–37]. There were no significant differences in AEs between EC and control groups in two randomized trials [76,77]. There were no SAEs in one trial [77], and in the other SAEs were considered to be unrelated to the products under study [76].

Among reports from 481 EC users on online forums that had sections dedicated specifically to the reporting of adverse health effects of EC use, the most common AEs were effects on the mouth and throat (around 50% of events) [78]. An increase in blood pressure, a potentially more concerning effect, was reported by 2% of correspondents.

The US Food and Drug Administration Center for Tobacco Products (CTP) collects data regarding AEs from a variety of sources. Between 2008 and the first quarter of 2012, the CTP received 47 reports of AEs related to EC, eight of which were deemed serious. With the exception of two, no causality was attributed to the EC. The two were infant death caused by choking on an EC cartridge and facial burns caused by EC exploding [79]. We are aware of two further media reports of exploding EC [80,81].

Regarding AEs reported in the medical literature, an EC user developed lipoid pneumonia, which resolved when EC use ceased [82]. An elderly heavy smoker experienced three episodes of acute asymptomatic atrial fibrillation, each preceded by EC use. She stopped EC use and had no further episodes [83].

Regarding the cardiovascular effects of EC, nicotine in EC increases heart rate after overnight abstinence [72,73]. Short-term EC use does not adversely affect haematological or blood chemistry parameters, or cardiovascular function in smokers or ex-smokers [84–87].

Regarding effects on respiratory function, 5 minutes of EC use generated an increase in airways resistance, associated with a 16% decrease in fractional exhaled nitric oxide (FeNO), a marker of bronchial inflammation, with no change in the control group. These effects were not considered clinically significant [59].

In another study, smoking a cigarette led to a significant reduction in forced expiratory volume in 1 second/forced vital capacity (FEV_1/FVC), while EC use generated no acute change in lung function. There were no significant changes in FeNO in either group [69].

Risks of nicotine poisoning

A claim is often repeated that an ingestion of 30–60 mg of nicotine is fatal [88], but this assertion is based on dubious self-experiments in the 1890s [89]. Tobacco and NRT have been available to hundreds of millions of people, but fatal poisoning by nicotine is extremely rare. We are aware of one newspaper report of a fatal poisoning of a 2-year-old child who drank e-liquid [90] and of one case study on an 18-month-old child who drank e-liquid, was admitted to hospital with vomiting, ataxia and lethargy, and was discharged after 24 hours of observation [91]. With the increase in EC use, there has been an increase in calls to poison centres following accidental exposures, but these remain lower than calls following such exposure from tobacco and none resulted in any serious harm [92]. Several suicide attempts were recorded where adults drank up to 1500 mg of nicotine in e-liquid, which resulted in vomiting but recovery within a few hours [93].

Summary

Although surveys of users, prospective clinical studies and randomized controlled trials to date have not found any SAEs, several such events have been reported as case studies and in the media. Given the high media interest in EC, the number of such reports is remarkably low. Data to date show that EC pose a minimal risk of nicotine poisoning from the device as intended to be used, but e-liquid can be dangerous or lethal if ingested, particularly by small children.

EFFECTS ON SMOKERS

Nicotine levels in EC users

Early studies using brief fixed puffing schedules and smokers naive to EC use found low or no nicotine delivery [64,68,71]. With greater familiarity with the device and less restricted use, plasma nicotine delivery was comparable to that from oral NRT products (4–5 ng/ml) [3,70,73]. Some experienced EC users achieve nicotine

levels which are close to those obtained from smoking, but only after extended EC use (up to 14 ng/ml after 60 minutes of *ad libitum* use [33,65,72,94] compared with 10–20 ng/ml after smoking a cigarette) [95,96]. Importantly, users experienced in using the same model differed in how much nicotine they extracted from it [65]. As with cigarettes, user behaviour is an important factor in nicotine delivery.

Effects of EC use on withdrawal symptoms and on smoking behaviour

Using EC after overnight abstinence from smoking significantly reduces urges to smoke within 5–30 minutes [64,66–68,71,73]. Non-nicotine EC can also have this effect [64,66,67].

Three small studies evaluated the effects of EC in smokers not intending to reduce or quit smoking. They reported a ≥50% reduction in smoking at the end of 1 week in 32% of participants, including 14% who stopped smoking altogether [70]; sustained ≥50% reduction in 28% of participants and additional 13% abstinence rate at 2 years [75,97]; and ≥50% reduction in 50% of participants and additional 14% abstinence rate at 1 year in smokers with schizophrenia [74].

Data from representative surveys [19], surveys of EC users [3,4,24,34–37,39] and from clinical trials [45,74–77,97,98] show consistently that smokers who use EC and smoke at the same time (so called dual users) reduce their cigarette consumption.

Effects of EC on smoking cessation

Several case studies reported the benefits of EC in helping people who have failed to quit with other methods [99–101].

Several studies evaluated relationships between EC use and smoking reduction and cessation. Among the general population, EC users and non-users had the same quit rate, but EC use was associated with a significant reduction in cigarette consumption [19]. Among callers to a quitline, those who ever used EC compared with other callers had more previous failed quit attempts, were more likely to live with smokers and were less likely to quit at the current quit attempt [102]. The finding is due probably to bias by intention—more dependent smokers who choose to use EC and are also less likely to quit smoking. Similar findings have been observed with NRT [103]. One other study was interpreted as showing that EC use inhibits cessation, but another interpretation is that it showed that EC use is related to smoking history [104]. Adolescents who tried cigarettes at least once but are not smoking now were less likely to ever try EC than adolescents who smoke. In two cohorts, smokers who have tried EC had a similar likelihood of quitting as other smokers [19,21], but in a large population sample, smokers attempting to stop smoking with the help of EC were more likely to succeed than those using NRT bought from a store (without any professional supervision) or trying to quit unaided [105].

Among 'dual users', 46% quit smoking altogether after 1 year [106].

A randomized trial of 300 smokers not intending to quit compared the effects of two nicotine-containing and a nicotine-free EC provided for 12 weeks. The study used an EC with poor nicotine delivery that often malfunctioned and was subsequently discontinued [77]. At 1 year, smoking abstinence rates were 13, 9 and 4% in the three groups, respectively. There were no differences in smoking reduction in those who continued to smoke. The two nicotine EC groups merged had a higher quit rate than the non-nicotine group (11 versus 4%, $P = 0.04$).

A randomized trial in 657 treatment-seeking smokers compared EC with nicotine patches (21 mg) and with non-nicotine EC. The study used EC with low nicotine delivery [76]. Participants received a referral to a telephone quitline but no face-to-face contact. In this minimal support context, biochemically validated continuous abstinence rates at 6 months were 7.3, 5.8 and 4.1% in the three groups, respectively [not significant (NS)]. While the results were suggestive of a benefit for EC users, the study did not have adequate power to detect what would be a realistic margin of difference from the two active comparators. EC generated significantly higher self-reported smoking reduction and higher user endorsements than patches.

In the United Kingdom, where the use of EC to assist smoking cessation has now overtaken use of NRT, and detailed figures are available on month-to-month changes in smoking behaviour, the rise in EC use has been accompanied by an increase in successful quit attempts [107] and a continuing decrease in smoking prevalence [108].

Summary

EC reduce urges to smoke and there is preliminary evidence that EC use facilitates both quitting and reduction in cigarette consumption in smokers interested in quitting smoking. In England, which has the most detailed data on EC and cigarette use, the growth in EC use has been accompanied by an increase in smoking cessation rates, a continued reduction in prevalence and no increase in smoking uptake [107,108]. Whether EC are contributing to these favourable tobacco control trends is as yet unclear.

CONCLUSIONS

Important regulatory verdicts are being currently made and science-based decisions are needed to maximize

benefits and minimize risks to public health. The key issue to consider is whether EC use is likely to increase or decrease smoking-related morbidity and mortality. There are several hypothetical routes to a negative outcome and one route to a positive outcome. The reviewed evidence can contribute to their assessment. EC would generate negative outcomes if:

- Chemicals in EC cause excess morbidity and mortality. *Evidence*: health effects of long-term EC use are currently not known and a degree of risk may yet emerge. However, based on the data available regarding the toxicant content of EC liquid and aerosol, long-term use of EC, compared to smoking, is likely to be much less, if at all, harmful to users or bystanders. This is because unlike cigarettes, EC do not deliver combustion-generated toxicants that are linked to cancer, chronic lung disease and cardiovascular disease (CVD).
- Smokers who would otherwise quit combine EC and cigarettes instead of quitting and maintain a similar smoking rate. *Evidence*: EC use is associated with smoking reduction and there is little evidence that it deters smokers interested in stopping smoking tobacco cigarettes from doing so.
- Young people who would not try cigarettes otherwise start using EC and then move on to become smokers. *Evidence*: although there have been claims that EC is acting as a 'gateway' to smoking in young people, the evidence does not support this assertion. Regular use of EC by non-smokers is rare and no migration from EC to smoking has been documented (let alone whether this occurred in individuals not predisposed to smoking in the first place). The advent of EC has been accompanied by a decrease rather than increase in smoking uptake by children [109]. Ongoing surveillance is needed to address this important point.
- EC use will increase smoking prevalence indirectly, e.g. by making smoking acceptable again in the eyes of people who cannot tell the difference between EC and cigarettes, via machinations of the tobacco industry, or by weakening tobacco control activism. *Evidence*: there are no signs that the advance of EC is increasing the popularity of smoking or sales of cigarettes.

There is one hypothetical route to the positive outcome, i.e.:

- That EC reduce harm at the individual and population level by reducing cigarette use. In the most optimistic scenario, EC would continue to improve in providing smokers with what they want from their cigarettes, until the use of conventional cigarettes virtually disappears. *Evidence*: EC reduces cigarette use by facilitating smoking reduction and cessation on individual level, but the prevalence of EC use has been low until recently and the effect of EC use on cigarette consumption on the population level has not been established so far.

Implications for policy makers

The European Parliament has recently rejected a proposal to licence EC as medicines. There is a concern that medicinal regulation would disadvantage EC compared to cigarettes, make them more expensive, stifle their development and may drive them fully into the arms of the tobacco industry as the only player able to afford the large entry barriers [12,110]. In Europe, EC are subject to consumer protection legislation, and most countries are likely to ban sales to people under 18, as has recently been introduced in the United Kingdom. Advertising restrictions are also forthcoming [111,112]. Some regulators, however, believe these actions are not sufficient because of the hypothetical routes to negative outcomes discussed above. Regulatory decisions will provide the greatest public health benefit when they are proportional, based on evidence and incorporate a rational appraisal of likely risks and benefits.

Implications for researchers

Our review points to two key research priorities. One is ongoing surveillance of the temporal relationship between country-specific markers of EC use and smoking behaviour. Close monitoring, for which some instruments already exist [113–115], is needed to track changes in EC use and smoking prevalence. Sales data will also be informative; if increased EC sales are accompanied by an increase in cigarette sales, EC could be re-normalizing smoking and further regulatory steps would be required, while if they are associated with a decrease in cigarette sales, this would indicate a public health benefit of liberal regulation. The second priority concerns EC safety. Epidemiological studies are required that compare health outcomes in cohorts of regular EC users (who either use only EC or both EC and cigarettes) with matched cohorts of smokers and non-smokers. These need to be supplemented by laboratory and clinical studies of EC contents and effects on smoking behaviour.

Implications for health professionals

While there is not yet conclusive evidence about the effectiveness of e-cigarettes to generate smoking cessation or reduction, health-care professionals (HCP) should support smokers unable or unwilling to stop tobacco use who wish to switch to EC to reduce harm from smoking. HCP should emphasize the importance of stopping using cigarettes and nicotine altogether.

Declaration of interests

P.H., N.B. and T.E. have no links with any e-cigarette manufacturer. J.F.E. was reimbursed by a manufacturer of e-liquids for travelling to London and to China. H.M. was

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