Is there a role for e-cigarettes in smoking cessation?

Charlotte Leduc and Elisabeth Quoix

Abstract: The use of e-cigarettes has dramatically increased over the past few years and their role in smoking cessation remains controversial. Several clinical studies have evaluated their efficacy in smoking cessation but most of them are prospective cohort studies. Only two randomized, controlled trials have compared e-cigarettes versus placebo or patches. A meta-analysis of these two randomized, controlled trials has been performed. Nicotine-containing e-cigarettes appear to help smokers unable to stop smoking altogether to reduce their cigarette consumption when compared with placebo. However, these results are rated ‘low’ by GRADE standards. Many cohort studies have been conducted, with contradictory results. For some, e-cigarettes could increase the risk of nonsmokers developing nicotine dependence and of current smokers maintaining their dependence. The debate remains open and more randomized trials are needed with long-term data about the efficacy and safety of e-cigarettes.

Keywords: e-cigarette, nicotine replacement therapy, smoking cessation

Introduction

The use of the electronic cigarette (EC) has dramatically increased in popularity in numerous countries. This development has led to quite a lot of interrogations and controversies regarding its use in the context of mounting tobacco-smoking restrictions in most developed countries.

Should ECs be considered as a nicotine replacement therapy (NRT) or as a reduction of risk compared with tobacco products, or rather as a harmful device with consequences similar to tobacco use? Correct categorization of ECs is not easy; however, European and US Food and Drug Administration (FDA) regulations seem to classify ECs as a tobacco product.

The European directive 2014/40/EU dated 3 April 2014 (see http://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:32014L0040&from=FR), states regulations related to all tobacco products including ECs. It stipulates that the level of nicotine should be lower than 20 mg/ml. Only electronic devices delivering consistent levels of nicotine should be approved to avoid the risks of accidental consumption of high doses. However, this directive does not aim at harmonizing all rules, i.e. those related to flavor composition, age limit, presentation and advertising. In France, for example, the sale of ECs is not authorized to minors.

The FDA regulation of ECs is still on the way (see the FDA news release 24 April 2014, available at http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm394667.htm). At this time it is proposed to extend its authority to cover ECs in addition to tobacco products.

The World Health Organization has given definitive advice to smokers not to use ECs in September 2014 [WHO report, 2014]; the majority of scientific medical societies advocated this.

Unfortunately, it seems that passion outweighs the necessary objective vision, such as that provided by scientific studies, at this time. This article aims to review the role of ECs in smoking cessation and does not address safety.

What are electronic cigarettes?

The concept of the EC is quite old. The first one was developed in 1963 by Herbert A. Gilbert with a license under the name of ‘smokeless non tobacco cigarette’[patent no. US3200819]. However, it
was never commercialized. The first public device was patented in 2003 by Hon Lik [Cahn and Siegel, 2011] with an ultrasound technology for vaporization. The device was first commercialized in China under the auspices of the Golden Dragon holdings. The name of the society was then modified in 2010 to Ruyan, which means ‘like a cigarette’ in Chinese. In fact, most ECs nowadays are manufactured in China. The technology of vaporization through a heating resistance was developed in 2009, and commercialized as an electronic nicotine delivery system (ENDS) by David Yunqiang Xiu.

An EC is a battery-powered vaporizer producing an aerosol with a heating element that atomizes a liquid solution. The concept is to deliver nicotine with fewer toxicants and carcinogens than combusting cigarettes. The e-liquids usually contain a mixture of propylene glycol, glycerin, and various flavorings with or without nicotine. Nicotine content has to be lower than 20 mg/ml. A sensor detects when the user takes a puff, activating an electric coil to heat and vaporize the liquid, creating a visible cloud of vapor. A microprocessor controls the heat, and the vaporization occurs at a low temperature thanks to the properties of propylene glycol with or without glycerin. The e-liquid is inside a cartridge, which can be replaced. A rechargeable lithium-ion battery is part of the device.

Clinical studies evaluating the role of ECs in smoking cessation

Several clinical studies have evaluated the efficacy of ECs in smoking cessation but most of them are prospective cohort studies. Only two randomized, controlled trials (RCTs) have compared EC versus placebo or patches.

**RCTs**

Two RCTs have been conducted, one on smokers with no intention to quit and one on smokers who were motivated to quit (Table 1). The first, the ECLAT study, was an Italian prospective 12-month double-blind RCT. A first-generation EC was compared with placebo in 300 smokers not currently attempting to quit [Caponnetto et al. 2013b]. The inclusion criteria were: smoking at least 10 cigarettes per day for the past 5 years; being between 18 and 70 years old; having a good health status; and not using smokeless tobacco or an NRT. Subjects were randomized into three arms: (A) receiving 12 weeks of 7.2 mg nicotine cartridges; (B) receiving 6 weeks of 7.2 mg nicotine cartridges and a further 6 weeks with 5.4 mg nicotine cartridges; and (C) receiving 12 weeks of no-nicotine cartridges. Participants in each group were prospectively followed for 52 weeks. Smoking habits, exhaled carbon monoxide (eCO) levels, adverse events, vital signs, and product preferences were assessed at each study visit. The aim of the study was to assess the efficacy (smoking reduction and abstinence) and the safety of ECs. A significant reduction of the median number of cigarettes per day used from baseline was observed in all three groups: the median values were 19 for (A), 21 for (B) and 22 for (C) at baseline. There was a statistically significant reduction in the median number of cigarettes per day in arms (A) and (B) compared with (C) at weeks 2 (p = 0.04), 6 (p = 0.01) and 8 (p = 0.04). After 12 weeks, the median values

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>n</th>
<th>Motivated to quit</th>
<th>Experimental arm</th>
<th>Control arm</th>
<th>Follow up (month)</th>
<th>Relative risk (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullen et al. [2013b]</td>
<td>3 arms RCT 4:4:1</td>
<td>657</td>
<td>Yes</td>
<td>Nicotine EC (n = 289)</td>
<td>Placebo EC (n = 73)</td>
<td>6</td>
<td>1.77 (0.54–5.77)</td>
<td>No difference in abstinence rate among groups</td>
</tr>
<tr>
<td>Caponnetto et al. [2013b]</td>
<td>3 arms RCT 1:1:1</td>
<td>300</td>
<td>No</td>
<td>Nicotine EC (n = 200)</td>
<td>Placebo EC (n = 100)</td>
<td>12</td>
<td>2.75 (0.97–7.76)</td>
<td>No difference with or without nicotine</td>
</tr>
</tbody>
</table>

CI, confidence interval; EC, electronic cigarette; RCT, randomized, controlled trial.
were 11 for (A), 10 for (B) and 12 for (C). After 52 weeks, they were 12 for (A), 14 for (B) and 12 for (C). Similarly, a significant reduction in eCO levels from baseline was observed at each study visit in all three study groups but significant between-group differences were only observed at week 6 ($p = 0.01$). The median eCO values (ppm) were 16.0 for (A), 17.0 for (B) and 17.5 for (C) at 12 weeks ($p = 0.48$), and 15.0 for (A), 16.0 for (B) and 17.0 for (C) at 52 weeks ($p = 0.93$). ECs did not significantly reduce the number of smokers: at 12 and 52 weeks, quitters were, respectively, 11 (13%) in (A), 17 (9%) in (B), and 4 (4%) in (C). The most frequent adverse events (AEs) were: dry cough (26%), mouth irritation (22%), shortness of breath (20%), throat irritation (17%), and headache (17%). There was no difference between the three groups. However, the authors observed a significant reduction in the frequency of reported symptoms compared with baseline.

The second RCT is the ASCEND trial [Bullen et al. 2013a, 2013b], which randomized 657 adult New Zealanders, smoking 10 or more cigarettes per day, into three groups: a nicotine ECs treatment group (12 weeks of ECs with 16 mg/ml nicotine cartridges ad libitum), a placebo ECs control group (12 weeks of ECs without nicotine cartridges ad libitum), and a nicotine patch control group (21 mg nicotine patch daily). In this trial, participants wanted to quit smoking. The aim of the trial was to assess the effectiveness, acceptability, pattern of use, and safety of ECs for smoking cessation. The primary outcome was the proportion of participants for whom continuous abstinence was maintained for 6 months, which was 7.3% in the nicotine group, 5.8% in the patches group, and 4.1% in the placebo group. The difference was not significant ($p = 0.44$). In the nicotine EC group, 57% of participants reduced daily cigarettes by at least half at 6 months versus 41% in the patches group (41%, $p = 0.0002$). There was no significant difference compared with the placebo group (45%, $p = 0.08$). In this study, nicotine ECs appeared to be as effective as patches for achieving cessation at 6 months [relative risk (RR) = 1.26, 95% confidence interval (CI) 0.68–2.34]. There was no difference between the nicotine-containing EC and patches concerning adverse events (incidence rate ratio 1.05, 95% CI 0.82–1.34, $p = 0.7$). The authors conclude that nicotine ECs were at least as effective as patches for achieving cessation at 6 months.

A meta-analysis of these two RCTs was performed by the Cochrane Collaboration [McRobbie et al. 2014]. Use of a nicotine-containing EC was associated with higher abstinence rates than placebo EC use ($n = 662$, RR 2.29, 95% CI 1.05–4.96). Use of a nicotine-containing EC was also associated with a significantly higher likelihood of halving cigarette consumption than placebo EC ($n = 612$, RR 1.31, 95% CI 1.02–1.68). However, these results are based on only two trials, with low event rates and wide confidence intervals around the estimates mean. Consequently, they are rated ‘low’ by GRADE standards. Furthermore, inclusion criteria were not the same in the two trials, particularly concerning the motivation to quit smoking. ECs when compared with placebo and patches appear to help smokers unwilling to quit, but the above limitations also affect this finding.

For some authors, the EC lack of efficacy may be due to the fact that ECs used in these RCTs provided a slow delivery and a low dose of nicotine [Lopez and Eissenberg, 2015].

**Observational cohort studies**

Many cohort studies have attempted to evaluate the use of the EC as a smoking cessation tool in various populations, with various methods, and therefore with contradictory results. Most of them are longitudinal surveys, based on self-declared data, with all their limitations. Studies and their main results are summarized in Table 2.

A large proportion of studies have demonstrated an increase of cessation rate. In a longitudinal internet survey of 477 EC users, Etter and Bullen observed smoking cessation in 22% of those who were vaping daily at baseline, after 1 month, and 46% after 1 year [Etter and Bullen, 2014]. Polosa and colleagues conducted a prospective study and monitored modifications in smoking habits in 40 smokers unwilling to quit. ECs facilitated achieving abstinence in 22.5% of patients at week 24 [Polosa et al. 2014]. Caponnetto and colleagues conducted a similar study in 14 smokers with schizophrenia not intending to quit. Sustained abstinence from smoking occurred in two patients (14.3%) and a sustained 50% reduction in the number of cigarettes per day was shown at week 52 (from a median of 30 cigarettes per day to a median of 15 per day). As a consequence, a specific RCT for schizophrenic patients has been proposed to evaluate a more than or equal to 50%
Table 2. Cohort studies evaluating the efficacy of ECs in smoking cessation.

<table>
<thead>
<tr>
<th>Study</th>
<th>Study type</th>
<th>n*</th>
<th>Wanted to quit?</th>
<th>Intervention</th>
<th>Follow up (month)</th>
<th>Assessment</th>
<th>Abstinence rate (%)</th>
<th>OR (95% CI)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caponnetto et al. [2013a]</td>
<td>Prospective cohort</td>
<td>14</td>
<td>No</td>
<td>Nicotine EC</td>
<td>12</td>
<td>Exhaled CO</td>
<td>14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adkison et al. [2013]</td>
<td>Cross-sectional survey</td>
<td>450</td>
<td>Both</td>
<td>None</td>
<td>12</td>
<td>SR</td>
<td>11</td>
<td>0.81 (0.43–1.53)</td>
<td>No difference between EC users and non users</td>
</tr>
<tr>
<td>Popova and Ling [2013]</td>
<td>Cross-sectional survey</td>
<td>369</td>
<td>Both</td>
<td>None</td>
<td>12</td>
<td>SR</td>
<td>17</td>
<td>0.69 (0.52–0.94)</td>
<td></td>
</tr>
<tr>
<td>Vickerman et al. [2013]</td>
<td>Longitudinal survey</td>
<td>852</td>
<td>ND</td>
<td>None</td>
<td>7</td>
<td>SR</td>
<td>22</td>
<td>0.50 (0.40–0.63)</td>
<td>EC users were less likely to quit compared with never-users</td>
</tr>
<tr>
<td>Choi and Forster [2014]</td>
<td>Longitudinal survey</td>
<td>346</td>
<td>ND</td>
<td>None</td>
<td>12</td>
<td>SR</td>
<td>11</td>
<td>0.93 (0.19–4.63)</td>
<td></td>
</tr>
<tr>
<td>Grana et al. [2014b]</td>
<td>Longitudinal web-based survey</td>
<td>949</td>
<td>ND</td>
<td>None</td>
<td>12</td>
<td>SR</td>
<td>10</td>
<td>0.76 (0.36–1.60)</td>
<td></td>
</tr>
<tr>
<td>Grana and Benowitz [2014a]</td>
<td>Pooled analysis of (1–4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.61 (0.50–0.75)</td>
<td></td>
</tr>
<tr>
<td>Etter and Bullen, [2014]</td>
<td>Longitudinal internet survey</td>
<td>367</td>
<td>ND</td>
<td>None</td>
<td>12</td>
<td>SR</td>
<td>46</td>
<td></td>
<td>96% former smokers reported product helped them to quit; 67% used EC for withdrawal</td>
</tr>
<tr>
<td>Polosa et al. [2011]</td>
<td>Prospective cohort</td>
<td>40</td>
<td>No</td>
<td>Nicotine EC</td>
<td>24</td>
<td>Exhaled CO</td>
<td>13</td>
<td></td>
<td>No difference with NRT</td>
</tr>
<tr>
<td>Brown et al. [2014]</td>
<td>Cross-sectional survey</td>
<td>464</td>
<td>Yes</td>
<td>None</td>
<td>12</td>
<td>SR</td>
<td>20</td>
<td></td>
<td>EC was higher than NRT 10% or no aid 15%</td>
</tr>
<tr>
<td>Biener and Hargraves [2015]</td>
<td>Longitudinal survey</td>
<td>695</td>
<td>ND</td>
<td>None</td>
<td>6</td>
<td>SR</td>
<td></td>
<td></td>
<td>Daily use of EC &gt; 1 month is associated with quitting</td>
</tr>
</tbody>
</table>

*Only EC users.
ND, not defined; SR, self-reported; OR, odds ratio; CI, confidence interval; EC, electronic cigarette; NRT, nicotine replacement therapy.


Conclusion
In conclusion, there is a lack of data about the real role of ECs for long-term smoking abstinence. Thus, actual studies are insufficient to recommend or advise against the use of ECs as a smoking-cessation method. They suggest, however, that they might be used as an NRT. There is currently a huge controversy regarding the benefits and potential harms of ECs. Despite most international societies not recommending their use [Schraufnagel et al. 2014], the American Association for Cancer Research (AACR) and the American Society of Clinical Oncology (ASCO) recognize that the EC has the potential to alter patterns of tobacco use [Brandon et al. 2015]. More RCTs are needed to confirm EC efficacy, using the appropriate methodology to distinguish the impact of EC use both on cessation in a quit attempt, and as an alternative smoking pattern. Dual use of ECs and combustible cigarettes, as well as the combination of ECs and any FDA-approved cessation medication should also be studied, in order to evaluate the impact on cessation efforts and nicotine addiction.

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Conflict of interest statement
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References


Caponnetto, P., Campagna, D., Cibella, F., Morjaria, J., Caruso, M., Russo, C. et al. (2013b) EffiCiency

Some studies did not show the same results. Grana and colleagues [Grana et al. 2014a] have combined four longitudinal studies [Adkison et al. 2013; Vickerman et al. 2013; Grana et al. 2014b; Choi and Forster, 2014] and one cross-sectional study [Popova and Ling, 2013] in a random-effects meta-analysis in order to evaluate the role of the EC in smoking cessation. Using the EC was associated with a significantly lower chance of quitting smoking [pooled odds ratio (OR) = 0.61, 95% CI 0.50–0.75]. However, these studies were primarily designed to evaluate EC awareness, people’s knowledge, and smoking habits and cannot be considered as clinical trials but only as exploratory studies. For McMillen and colleagues, ECs could increase the risk of both nonsmokers developing nicotine dependence and current smokers maintaining their dependence [McMillen et al. 2012].

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