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

Ther Adv Respir Dis
2016, Vol. 10(2) 130–135
DOI: 10.1177/1753465815621233

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***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

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Table 1. Randomized, controlled trials evaluating the efficacy of EC in smoking cessation.

Study	Study type	*n*	Motivated to quit	Experimental arm	Control arm	Follow up (month)	Relative risk (95% CI)	Comments
Bullen *et al.* [2013b] (1)	3 arms RCT 4:4:1	657	Yes	Nicotine EC ($n = 289$)	Placebo EC ($n = 73$) Patch (n = 295)	6	1.77 (0.54–5.77) 1.26 (0.68–2.34)	No difference in abstinence rate among groups
Caponnetto *et al.* [2013b] (2)	3 arms RCT 1:1:1	300	No	Nicotine EC ($n = 200$)	Placebo EC ($n = 100$)	12	2.75 (0.97–7.76)	No difference with or without nicotine
McRobbie *et al.* [2014]	Meta-analysis of (1) and (2)	662	Both	Nicotine EC ($n = 389$)	Placebo EC ($n = 173$)		2.29 (1.05–4.96)	Quality of evidence: low

CI, confidence interval; EC, electronic cigarette; RCT, randomized, controlled trial.

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

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.

Study	Study type	*n**	Wanted to quit?	Intervention	Follow up (month)	Assessment	Abstinence rate (%)	OR (95% CI)	Comments
Caponnetto *et al.* [2013a]	Prospective cohort	14	No	Nicotine EC	12	Exhaled CO	14		
Adkison *et al.* [2013]	Cross-sectional survey	450	Both	None	12	SR	11	0.81 (0.43–1.53)	No difference between EC users and non users
Popova and Ling [2013] (4)	Cross-sectional survey	369	Both	None	12	SR	17	0.69 (0.52–0.94)	
Vickerman *et al.* [2013] (1)	Longitudinal survey	852	ND	None	7	SR	22	0.50 (0.40–0.63)	EC users were less likely to quit compared with never-users
Choi and Forster [2014] (3)	Longitudinal survey	346	ND	None	12	SR	11	0.93 (0.19–4.63)	
Grana *et al.* [2014b] (2)	Longitudinal web-based survey	949	ND	None	12	SR	10	0.76 (0.36–1.60)	
Grana and Benowitz [2014a]	Pooled analysis of (1–4)							0.61 (0.50–0.75)	
Etter and Bullen, [2014]	Longitudinal internet survey	367	ND	None	12	SR	46		96% former smokers reported product helped them to quit; 67% used EC for withdrawal
Polosa *et al.* [2011]	Prospective cohort	40	No	Nicotine EC	24	Exhaled CO	13		No difference with NRT
Brown *et al.* [2014]	Cross-sectional survey	464	Yes	None	12	SR	20		EC was higher than NRT (10%) or no aid (15%)
Biener and Hargraves [2015]	Longitudinal survey	695	ND	None	6	SR			Daily use of EC $>$ 1 month is associated with quitting

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

reduction in the number of cigarettes per day from baseline, the rate of abstinence from smoking [Caponnetto *et al.* 2014]. It is a prospective 12-month RCT comparing two different types of disposable ECs: high nicotine (24 mg) and no nicotine (with tobacco aroma) with a third arm being the use of the PAIPO nicotine-free inhalator (a plastic device resembling a cigarette and containing a sponge filter soaked in natural oil enriched with extracts of different aromas).

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].

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.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

Conflict of interest statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

References

Adkison, S., O'Connor, R., Bansal-Travers, M., Hyland, A., Borland, R., Yong, H. *et al.* (2013) Electronic nicotine delivery systems: international tobacco control four-country survey. *Am J Prev Med* 44: 207–215.

Biener, L. and Hargraves, J. (2015) A longitudinal study of electronic cigarette use among a population-based sample of adult smokers: association with smoking cessation and motivation to quit. *Nicotine Tob Res Off J Soc Res Nicotine Tob* 17: 127–133.

Brandon, T., Goniewicz, M., Hanna, N., Hatsukami, D., Herbst, R., Hobin, J. *et al.* (2015) Electronic nicotine delivery systems: a policy statement from the American Association for Cancer Research and the American Society of Clinical Oncology. *J Clin Oncol* 33: 952–963.

Brown, J., Beard, E., Kotz, D., Michie, S. and West, R. (2014) Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study: Real-world effectiveness of e-cigarettes. *Addiction* 109: 1531–1540.

Bullen, C., Howe, C., Laugesen, M., McRobbie, H., Parag, V., Williman, J. *et al.* (2013a) Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet* 16: 382: 1629–1637.

Bullen, C., Williman, J., Howe, C., Laugesen, M., McRobbie, H., Parag, V. *et al.* (2013b) Study protocol for a randomised controlled trial of electronic cigarettes versus nicotine patch for smoking cessation. *BMC Public Health* 13: 210.

Cahn, Z. and Siegel, M. (2011) Electronic cigarettes as a harm reduction strategy for tobacco control: a step forward or a repeat of past mistakes? *J Public Health Policy* 32: 16–31

Caponnetto, P., Auditore, R., Russo, C., Cappello, G. and Polosa, R. (2013a) Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study. *Int J Environ Res Public Health* 10: 446–461.

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

and safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PloS One* 8: e66317.

Caponnetto, P., Polosa, R., Auditore, R., Minutolo, G., Signorelli, M., Maglia, M. *et al.* (2014) Smoking cessation and reduction in schizophrenia (SCARIS) with e-cigarette: study protocol for a randomized control trial. *Trials* 15: 88.

Choi, K. and Forster, J. (2014) Beliefs and experimentation with electronic cigarettes: a prospective analysis among young adults. *Am J Prev Med* 46: 175–178.

Etter, J. and Bullen, C. (2014) A longitudinal study of electronic cigarette users. *Addict Behav* 39(2): 491–494.

Grana, R., Benowitz, N. and Glantz, S. (2014a) E-cigarettes: a scientific review. *Circulation* 129(19): 1972–1986.

Grana, R., Popova, L. and Ling, P. (2014b) A longitudinal analysis of electronic cigarette use and smoking cessation. *JAMA Intern Med* 174(5): 812–813.

Lopez, A. and Eissenberg, T. (2015) Science and the evolving electronic cigarette. *Prev Med* 80: 101–106. DOI: 10.1016/j.ypmed.2015.07.006. [Epub ahead of print 16 July 2015].

McMillen, R., Maduka, J. and Winickoff, J. (2012) Use of emerging tobacco products in the United States. *J Environ Public Health* 2012: 989474. DOI: 10.1155/2012/989474. [Epub ahead of print 10 May 2012].

McRobbie, H., Bullen, C., Hartmann-Boyce, J. and Hajek, P. (2014) Electronic cigarettes for smoking cessation and reduction. Cochrane Database of Systematic Reviews. Available at: http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD010216.pub2/pdf (accessed 23 November 2015).

Polosa, R., Caponnetto, P., Maglia, M., Morjaria, J. and Russo, C. (2014) Success rates with nicotine personal vaporizers: a prospective 6-month pilot study of smokers not intending to quit. *BMC Public Health* 14: 1159.

Popova, L. and Ling, P. (2013) Alternative tobacco product use and smoking cessation: a national study. *Am J Public Health* 103: 923–930.

Schraufnagel, D., Blasi, F., Drummond, M., Lam, D., Latif, E., Rosen, M. *et al.* (2014) Electronic cigarettes: a position statement of the forum of international respiratory societies. *Am J Respir Crit Care Med* 190: 611–618.

Vickerman, K., Carpenter, K., Altman, T., Nash, C. and Zbikowski, S. (2013) Use of electronic cigarettes among state tobacco cessation quitline callers. *Nicotine Tob Res Off J Soc Res Nicotine Tob* 15: 1787–1791.

WHO (2014) Electronic delivery systems. In: *Conference of the parties to the WHO framework on tobacco control*, Moscow, Russian Federation. Geneva: WHO.