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Evidence summaries

Electronic cigarettes for smoking cessation and reduction. Summary of the evidence and implications for public health programmes

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1. The evidence

A Cochrane systematic review identified eleven studies (2 RCTs involving 957 participants and nine Cohort studies involving 1993 participants) that gave electronic cigarettes (EC) to subjects, who were current smokers to help them stop smoking. The study settings were varied from the USA, Europe, and South Africa and some were online surveys (from Europe).

The RCTs found study found some evidence that participants using an EC were more likely to have abstained from smoking for at least six months compared with participants using placebo EC. However the GRADE of evidence was low.

The one study that compared EC to nicotine patch found no significant difference in six-month abstinence rates, again with very low GRADE evidence. A higher number of people were able to reduce cigarette consumption by at least half with ECs compared with placebo ECs and nicotine patch, again with low and very low GRADE of evidence.

The Cohort studies showed that ECs did reduce abstinence at 6, 12, 18 and 24 months as well as a ≥50% reduction of baseline cigarette consumption at the same time periods. The review did not find any increase in serious adverse events comparing ECs with placebo or nicotine patch.

The review concluded that ECs help smokers to stop smoking long-term compared with placebo ECs. It did not find

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Table 1 – Summary and critical appraisal of the systematic review.

	What did the review authors search for?	What did the review find?
Types of studies	<p>1. Randomized controlled trials, in which smokers are randomized to ECs or to a control condition, which measure abstinence rates or changes in cigarette consumption at six months or longer.</p> <p>2. Randomized cross-over trials and cohort follow-up studies with follow-up of greater than a week, for assessment of adverse events.</p>	<p>Two RCTs (662 participants) met the inclusion criteria for the primary outcome.</p> <p>Two RCTs and 11 cohort studies (1090 patients) met the inclusion criteria for adverse events.</p>
Setting	The authors looked for interventions from countries irrespective of economic strata and irrespective of the patients clinical setting.	<p>The two RCTs were from community setting in Italy and New Zealand.</p> <p>The cohort studies were mostly from Europe.</p>
Participants	<p>People defined as current smokers at enrolment into the trial.</p> <p>Participants can be motivated or unmotivated to quit.</p>	<p>One RCT from New Zealand were motivated to quit. The second RCT from Italy were those not motivated to quit.</p> <p>Some cohort studies had participants, who wanted to quit while others, who were not motivated or, who had tried to quit and failed.</p>
Interventions	They compared ECs with placebo ECs, ECs versus alternative smoking cessation aids, including NRT or no intervention, and ECs added to standard smoking cessation treatment (behavioral or pharmacological or both) with standard treatment alone.	<p>One RCT compared Elusion brand EC (first generation technology) with cartridges containing 16 mg nicotine, or 21 mg/24-h nicotine patches, or an EC with cartridges without nicotine (placebo EC), for 12 weeks following a target quit date (TQD). The ECs were couriered to participants, and those allocated to the patch arm were mailed a voucher to exchange for NRT at a pharmacy. All participants received an invitation to access phone- or text-based support, although this was accessed by fewer than 10%. The EC used in this study delivered only low levels of nicotine.</p> <p>The second RCT had three arms with Categoria brand EC with disposable cartridges containing 7.2 mg nicotine or 0 mg nicotine (placebo EC) for 12 weeks. The third arm used cartridges containing 7.2 mg nicotine for six weeks followed by 5.2 mg nicotine for another six weeks.</p> <p>The prospective cohort studies had different brands of EC with different concentrations of nicotine. The other observational studies were surveys, which did not mention the type of EC.</p>
Outcomes	<p>Primary outcomes</p> <p>Cessation at the longest follow-up point, which was at least six months from the start of the intervention, measured on an intention-to-treat basis using the strictest definition of abstinence, preferring biochemically validated results were reported.</p> <p>Secondary outcomes</p> <p>Reduction in cigarette use at the longest follow-up point, which was at least six months from the start of the intervention, measured on an intention-to-treat basis confirmed by a reduction in biomarkers of exposure (e.g., carbon monoxide, thiocyanate, and other markers of tobacco use), if reported.</p> <p>Adverse events</p> <p>Data were collected from both RCT as well as the observational studies on any adverse events at one week or longer, serious and non-serious, from the included studies.</p>	<p>Both the RCTS as well as the observational studies presented data on abstinence rates as well as reduction in use.</p> <p>Adverse events were mentioned in the results of the RCTs as well as observational studies.</p>

Table 1 (Continued)

	What did the review authors search for?	What did the review find?
Date of the last search: 25 September 2014		
Funding sources: Queen Mary University of London, UK and the University of Auckland, New Zealand provided salary, office space and library resources for the authors. Some authors had received funding from EC manufacturers, which they declared.		
What were the effects Electronic cigarettes on smoking cessation versus placebo from the RCTs	In the two studies (662 patients) there was a significant reduction in smoking RR 2.29, 95%CI (1.05–4.96). However the GRADE quality of evidence was low, due to indirectness of evidence as in one trial the EC had very low dose nicotine and imprecision as the number of events were low overall. There was no heterogeneity in the results.	
What were the effects Electronic cigarettes on smoking cessation versus nicotine replacement therapy from the RCTs	One study (584 patients) showed no significant difference RR1.26 95%CI (0.68–2.34) with very low quality evidence by GRADE.	
What were the effects Electronic cigarettes on smoking reduction (50% reduction from baseline) versus placebo from the RCTs	In the two studies (662 patients), there was a significant reduction in smoking RR 1.31, 95%CI (1.02–1.68). However the GRADE quality of evidence was low, due to indirectness of evidence as in one trial the EC had very low dose nicotine and imprecision as the number of events were low overall.	
What were the effects Electronic cigarettes on smoking reduction (50% reduction from baseline) versus nicotine replacement therapy from the RCTs	One study (546 patients) showed significant difference RR1.41 95%CI (1.20–1.67) with very low quality evidence by GRADE. It was downgraded one level due to indirectness. The electronic cigarette used in the study was not very effective at delivering nicotine. It was also downgraded two levels due to imprecision. Only one included study, with small number of events in each arm.	
What were the effects Electronic cigarettes on smoking cessation among observational studies	One prospective Cohort with patients motivated to quit smoking found 44% (21/48) abstinent at 6 months among the EC users. In two prospective cohorts of unmotivated subjects the abstinence rate was 23% (9/40) at 6 months and 15% (6/40) and 13% (5/40) respectively at 18 and 24 months.	
What were the effects Electronic cigarettes on smoking reduction (50% reduction from baseline) among observational studies	One prospective Cohort with patients motivated to quit smoking found 27% (13/48) reduced by 50% at 6 months among the EC users. In two prospective cohorts of unmotivated subjects the rate was 33% (13/40) at 6 months and 28% (11/40) at 18 and 24 months.	
What were the effects Electronic cigarettes on harmful side effects	None of the RCTs or cohort studies reported any serious adverse events (SAEs) that were considered to be plausibly related to EC use. Mouth and throat irritation being the most frequently reported AEs in EC users.	
What were the effects Electronic cigarettes on smoking cessation among RCT and observational studies	Among 1090 (8 studies: 2 RCTs, 6 cohort) none reported any serious AEs that were related to EC use. Neither RCT detected a significant difference in AEs between intervention and control groups. Cohort studies found mouth and throat irritation, dissipating over time, to be the most frequently reported AEs in EC users. The quality of the evidence was rated as low due to risk of bias as 6 of 8 were cohort studies and imprecision as only one trial compared EC with nicotine replacement therapy.	
What were the conclusions of the review?	The review concluded that “There is evidence from two trials that ECs help smokers to stop smoking long-term compared with placebo ECs. The lack of difference between the effects of ECs compared with nicotine patches found in one trial is uncertain. ECs appear to help smokers unable to stop smoking altogether to reduce their cigarette consumption, when compared with placebo ECs and nicotine patches. No evidence emerged that short-term EC use is associated with health risk.” “However, the small number of trials, low event rates and wide confidence intervals around the estimates mean that our confidence in the result is rated ‘low’ by GRADE standards.”	
What were the assessments of the overall quality of the evidence?	The study quality was assessed using the Cochrane risk of bias tool, which looks at the randomization process, allocation concealment, blinding, completeness of outcome data and possible selective reporting. Both RCTs were evaluated to have low overall risk of bias. One RCT had 22% lost to follow-up rate. Non-RCTs The observational studies by nature of design were categorized as being at high risk of selection bias. The three surveys did not validate self-reported abstinence, excluded EC users, who stopped smoking, and two do not provide a clear definition of abstinence. The lack of intervention or contact with researchers means that there is unlikely to be a significant performance or detection bias. The Five cohort studies included biochemical validation of participants and so were graded as being at low risk of detection bias. Rates of follow-up were mixed-one followed up all participants, while another had one-year data from only 367 (28%) of the 1329 people that completed the baseline survey. For many of the cohort studies the authors were unable to determine prespecified outcomes and hence rated these as being at unclear risk of reporting bias. One did not provide a definition of abstinence and it was unclear if the completion of the programme was at six months after enrolment, or at an earlier time point.	

Table 1 (Continued)

	What did the review authors search for?	What did the review find?
Strengths and limitations	The strengths of the review include following the Cochrane methods rigorously and including both RCT as well as observational studies. Overall the quality of the evidence appeared to be low. The studies were from developed countries only. The limitations include the small number of studies and study participants in the RCT and inadequate data from both RCT and observational studies to assess all outcomes that were planned.	
Did the results and conclusions of the review differ from other reviews on this topic?	The results of this systematic review are similar to another comprehensive review that suggested benefit. ³ A large population survey ⁴ of that had smoked within the previous 12 months and made at least one quit attempt during that period found that attempting to stop smoking with the help of ECs were more likely to succeed than those using NRT or trying to quit unaided. This benefit remained after adjusting for confounders, including nicotine dependence. A World Health Organization review ⁵ which pooled data from five population-based studies (four longitudinal and one cross-sectional) found EC use associated with a significantly lower chance of quitting smoking (OR 0.61, 95% CI 0.50–0.75). Three studies included in this review were not included in the present systematic review. One was ⁶ was cross-sectional, one ⁷ used a longitudinal design, participants were only asked about EC use at follow-up, and one ⁸ surveyed people at seven months after enrolment into a Quitline service and asked them about EC use retrospectively. The authors were unable to determine how much EC use occurred at baseline or how many clients used ECs as part of their quit attempt. Also, smokers calling the Quitline were those, who did not benefit from EC use and so this only included 'treatment failures' and cannot determine the effects of EC use overall.	
What further research is required?	Placebos EC provide a sensory-neural input along with being placebos. This may or may not reduce the impact of the EC with nicotine. Future studies should focus on comparing ECs with 'usual care' or minimal treatment, and with alternative pharmacological and behavioral treatments. Data are also needed on the proportions of smokers, who successfully quit smoking with the help of ECs and, who continue to use ECs long-term and the proportion, who eventually become nicotine-free. The ECs studied should have good nicotine delivery and be current with respect to reliability and user satisfaction. The trials should preferably be pragmatic trials and of adequate sample size to detect meaningful differences.	
What are the implications of the review for public health?	This systematic review suggests that ECs may have a role in helping chronic smokers quit smoking or reduce the usage by at least 50%. However, adequately powered, pragmatic trials including developing countries are required before ECs are suggested as a standard of care. We suggest they be advocated by physicians as part of research studies till more evidence is available.	

difference between EC and patch in this regard. It suggested that ECs appear to help smokers unable to stop smoking altogether to reduce their cigarette consumption, when compared with placebo ECs and nicotine patches. They found no evidence of harm with short term EC use. They, however, caution that the grade of evidence overall was low.

Review on which this evidence summary is based: McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database of Systematic Reviews* 2014, Issue 12. Art. No.: CD010216. DOI: [10.1002/14651858.CD010216.pub2](https://doi.org/10.1002/14651858.CD010216.pub2).

This evidence summary presents an overview of the findings and the implications for developed and developing countries. For further details, please read the full review that can be downloaded, free of charge (through various funded provisions) in most parts of the world, from *The Cochrane Library* (www.thecochranelibrary.com).

2. Why is this question important?

The use of tobacco including smoking cigarettes is among the major risk factors for noncommunicable diseases including cardiovascular, respiratory and cancers. Smoking cessation

rates by voluntary efforts are very poor.¹ Assisted methods such as behavioral interventions and nicotine patches and gums have poor long-term abstinence rates probably because of a lack of sensory and behavioral aspects associated with them.

In order to overcome this, EC, which are electronic vaporizing devices broadly similar in appearance to cigarettes and contain propylene glycol and glycerol, with or without nicotine and flavors have been tried. They provide sensations and experience similar to cigarettes.² Those that contain nicotine are called 'nicotine EC' and nicotine-free EC as 'placebo EC' in the review.

The EC are used for two reasons smoking cessation or reduction in smoking. The harmful effects of long-term use of ECs are also an issue to patients and health care providers.

3. What did the systematic review seek, and what did they find?

Review objectives. The objective is to evaluate the efficacy of EC for helping people, who smoke to achieve long-term abstinence (Table 1).

Conflicts of interest

The authors have none to declare.

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REFERENCES

1. Hughes JR, Keely J, Naud S. Shape of the relapse curve and long-term abstinence among untreated smokers. *Addiction*. 2004;99(January (1)):29–38.
2. Barbeau AM, Burda J, Siegel M. Perceived efficacy of e-cigarettes versus nicotine replacement therapy among successful e-cigarette users: a qualitative approach. *Addict Sci Clin Pract*. 2013;8:5.
3. Hajek P, Etter J-F, Benowitz N, Eissenberg T, McRobbie H. Electronic cigarettes: review of use, content, safety, effects on smokers, and potential for harm and benefit. *Addiction*. 2014;109(November (11)):1801–1810.
4. Brown J, Beard E, Kotz D, Michie S, West R. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. *Addiction*. 2014;109(September (9)):1531–1540.
5. Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. *Circulation*. 2014;129(May (19)):1972–1986.
6. Popova L, Ling PM. Alternative tobacco product use and smoking cessation: a national study. *Am J Public Health*. 2013;103(May (5)):923–930.
7. Adkison SE, O'Connor RJ, Bansal-Travers M, et al. Electronic nicotine delivery systems: international tobacco control four-country survey. *Am J Prev Med*. 2013;44(March (3)):207–215.
8. Vickerman KA, Carpenter KM, Altman T, Nash CM, Zbikowski SM. Use of electronic cigarettes among state tobacco cessation quitline callers. *Nicotine Tob Res Off J Soc Res Nicotine Tob*. 2013;15(October (10)):1787–1791.