Electronic cigarettes for smoking cessation

Results from the most recent Cochrane update

Jamie Hartmann-Boyce*, Hayden McRobbie, Chris Bullen, Rachna Begh, Lindsay F Stead, Peter Hajek

*Cochrane Tobacco Addiction Group, Nuffied Department of Primary Care Health Sciences, University of Oxford. Jamie.hartmann-boyce@phc.ox.ac.uk

8 March 2017
Acknowledgements

I am funded by the NIHR and have no conflicts of interest to declare.
What I’ll cover

General background

• Cochrane

EC for smoking cessation review

• Methods
• Results
• Other reviews
• Conclusions
About Cochrane

WHAT?
- Gathers and combines the best evidence from research to determine the benefits and risks of treatments/interventions

HOW?
- By systematically reviewing the available evidence, with strong emphasis on quality assessment

WHY?
- To help healthcare providers, patients, carers, researchers, funders, policy makers, guideline developers improve their knowledge and make decisions
Objective of this review

Evaluate the safety and effect of using EC to help people who smoke achieve long-term smoking abstinence
Inclusion criteria: study design

Randomized controlled trials
- Smokers randomized to EC or control

Uncontrolled intervention studies
- All people in the study offered EC

Won’t be included in next update due to nature of their design and risk of confounding
Inclusion criteria: participants

• People defined as current smokers at enrolment into study, motivated or unmotivated to quit
### Outcomes

<table>
<thead>
<tr>
<th>Cessation</th>
<th>Adverse events (AE)</th>
<th>Serious adverse events (SAE)</th>
<th>Changes in relevant biomarkers</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 months+</td>
<td>One week or longer of EC use</td>
<td>One week or longer of EC use</td>
<td>One week or longer of EC use</td>
</tr>
<tr>
<td>Intention to treat</td>
<td>Defined as any undesirable experience associated with the use of a medical product in a patient</td>
<td>Any AE where the patient outcome is death; life-threatening; hospitalization; disability; birth defect; or requires intervention to prevent any of the above</td>
<td>Known carcinogens</td>
</tr>
<tr>
<td>Strictest definition of abstinence</td>
<td>(as per standard Cochrane methods)</td>
<td></td>
<td>Exhaled carbon monoxide</td>
</tr>
<tr>
<td>Biochemically verified where available</td>
<td></td>
<td></td>
<td>Airway and lung function</td>
</tr>
<tr>
<td>(as per standard Cochrane methods)</td>
<td></td>
<td></td>
<td>Blood oxygen levels</td>
</tr>
</tbody>
</table>
Searches

- 7 electronic databases searched to Jan 2016
- Researchers contacted
- Trial registries & conference abstracts for ongoing studies
- In this update, screened 1117 references, full text of 49 articles
Screening and data extraction

• Followed standard Cochrane methods
• Done in duplicate by two independent reviewers
• Risk of bias assessed using Cochrane Risk of Bias Tool
Numerical analyses

- Pooled data where appropriate following standard Cochrane methods

\[
\text{Risk ratio} = \frac{\text{# of people quit in intervention group}/\text{# of people in intervention group}}{\text{# of people quit in control group}/\text{# of people in control group}}
\]

Risk ratio = 1 if no difference
< 1 if more people quit in control
> 1 if more people quit in intervention
Search results

- Included studies: 13
- Ongoing studies: 6
- Excluded studies: 39
<table>
<thead>
<tr>
<th>Included studies: RCTs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Caponetto 2013</strong></td>
</tr>
<tr>
<td>• 300 smokers not intending to quit</td>
</tr>
<tr>
<td>• EC with and without nicotine (one nicotine EC group reduced nicotine over time, combined with other nicotine group)</td>
</tr>
<tr>
<td>• 12 month follow-up</td>
</tr>
<tr>
<td><strong>Bullen 2013</strong></td>
</tr>
<tr>
<td>• 657 smokers wanting to quit</td>
</tr>
<tr>
<td>• EC with nicotine, EC without nicotine, NRT (patches)</td>
</tr>
<tr>
<td>• 6 month follow-up</td>
</tr>
</tbody>
</table>
### Included studies: observational data

<table>
<thead>
<tr>
<th>Intervention cohort (quit data)</th>
<th>Longitudinal surveys (quit data)</th>
<th>AE data</th>
</tr>
</thead>
<tbody>
<tr>
<td>• 7 studies (4 new)</td>
<td>• 8 studies (5 new)</td>
<td>• 9 report overall AE incidence</td>
</tr>
<tr>
<td>• Provided participants with EC and/or instructions on how to use EC to cut down or quit smoking</td>
<td>• Included smokers who had tried or used EC in past 6m</td>
<td>• 8 report effects on specific parameters</td>
</tr>
<tr>
<td></td>
<td>• Will be excluded in next update</td>
<td></td>
</tr>
</tbody>
</table>
## Risk of bias

<table>
<thead>
<tr>
<th>Study</th>
<th>Random sequence generation (selection bias)</th>
<th>Allocation concealment (selection bias)</th>
<th>Blinding of participants and personnel (performance bias)</th>
<th>Blinding of outcome assessment (detection bias)</th>
<th>Incomplete outcome data (attrition bias)</th>
<th>Selective reporting (reporting bias)</th>
<th>Other bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriaens 2014</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Al-Delaimey 2015</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
<tr>
<td>Borderud 2014</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Brose 2015</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>?</td>
<td></td>
</tr>
<tr>
<td>Bullen 2013</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Caponnetto 2013a</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
</tr>
</tbody>
</table>

---

*Note: + indicates low risk of bias; - indicates high risk of bias; ? indicates unclear risk of bias.*
Quitting at 6 months and longer, EC versus placebo

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Experimental Total</th>
<th>Control Events</th>
<th>Control Total</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>M-H, Fixed, 95% CI</td>
<td>M-H, Fixed, 95% CI</td>
</tr>
<tr>
<td>Caponnetto 2013a</td>
<td>22</td>
<td>200</td>
<td>4</td>
<td>100</td>
<td>2.75 [0.97, 7.76]</td>
<td></td>
</tr>
<tr>
<td>Bullen 2013</td>
<td>21</td>
<td>289</td>
<td>3</td>
<td>73</td>
<td>1.77 [0.54, 5.77]</td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>489</strong></td>
<td><strong>173</strong></td>
<td></td>
<td></td>
<td>2.29 [1.05, 4.96]</td>
<td></td>
</tr>
<tr>
<td><strong>Total events</strong></td>
<td>43</td>
<td></td>
<td>7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity</strong></td>
<td>Chi² = 0.30, df = 1 (P = 0.58); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect</strong></td>
<td>Z = 2.09 (P = 0.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GRADE quality of evidence: LOW (small number of studies, Bullen poor nicotine delivery)
Quitting at 6 months and longer, EC versus NRT

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Risk Ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bullen 2013</td>
<td>21</td>
<td>17</td>
<td>1.26 [0.68, 2.34]</td>
</tr>
</tbody>
</table>

GRADE quality of evidence: VERY LOW (only one study, issue with nicotine delivery)
Uncontrolled intervention studies

Percentage abstinent

Study ID

Polosa 2011 (6m)  Polosa 2014b (6m)  Ely 2013 (6m)  Polosa 2015 (6m)  Adriaens 2014 (8m)  Pacifici 2015 (1 year)  Caponetto 2013b (1 year)  Polosa 2015 (1 year)  Polosa 2011 (2 years)
Adverse events

- There were no serious adverse events related to EC use in any study
- Non-serious adverse effects did not differ between study arms: Bullen et al. 2013: nicotine EC 44%; patch 45%; placebo EC 47%
- Cohort studies similar, mouth and throat irritation most frequent AE, dissipating over time
- Longest use: 2 years

GRADE quality of evidence: LOW (small number of studies, cohort studies at high risk of bias)
## Impacts on specific parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Exhaled CO</strong></td>
<td>- 5 studies measured&lt;br&gt;- All found significant reductions over time&lt;br&gt;- Includes studies in dual users</td>
</tr>
<tr>
<td><strong>3-HPMA</strong></td>
<td>- Carcinogen in cigarette smoke&lt;br&gt;- 1 study measured&lt;br&gt;- Significant decline over 4 weeks EC use in single and dual users</td>
</tr>
<tr>
<td><strong>Airway and lung function</strong></td>
<td>- 2 studies measured, significant improvement (single &amp; dual users)&lt;br&gt;- 1 study measured blood oxygen levels, significant improvement after 2 wks EC use</td>
</tr>
</tbody>
</table>
Comparison with other reviews

Why do the RCTs provide different answers than the observational studies?

Many different reasons, including:
• variations in the effectiveness of ECs depending on the level of support provided
• issues around definitions of baseline EC usage
• unexplored confounders (not specific to EC – same has been found for NRT when we don’t control for confounders)
• studies which analyze results in smokers based on EC use at baseline have by the nature of their design already excluded people who have successfully quit using EC, and therefore only retain participants who, at entrance to the study, would be classed as 'treatment failures' or are in the midst of a cessation attempt involving cutting down to quit.

Following the standard methods of the Cochrane Tobacco Addiction Group and the protocol for this review, we focused on evidence from RCTs for cessation outcomes.
Implications for practice

- Limited number of RCTs have been reported, so certainty about the effects is low. More data are needed to strengthen confidence in the estimates.
- Evidence from the pooled results of two trials that EC with nicotine, compared with placebo ECs, helped smokers to stop smoking long-term. Corresponds to findings from placebo-controlled trials of NRT.
- Evidence from one trial that ECs may lead to six-month quit rates similar to those achieved with NRT, but the confidence interval is wide. ECs are an evolving technology and the effects of newer devices with better nicotine delivery are unknown.
- None of the included studies (up to two years) detected SAEs considered possibly related to EC use. The most commonly reported adverse effects were irritation of the mouth and throat. The long-term safety of ECs is unknown. In some studies, reductions in biomarkers were observed in smokers who switched to vaping consistent with reductions seen in smoking cessation.
Thank you

Jamie.hartmann-boyce@phc.ox.ac.uk
Uncontrolled intervention studies

- **Vape shops, Italy**
  - N = 71, first purchase at participating shop
  - Instructed how to fill, activate and use EC in anticipation of reducing cpd
  - 30 day PP, self-report

- **RCT but all participants provided EC at week 8**
  - N = 50, unmotivated to quit
  - Provided 2nd generation EC (18mg/ml nicotine) and instructions on use (control group didn’t receive instructions)
  - CO validated cessation, not defined

- **Smoking cessation clinic, Italy**
  - N = 50, unwilling to quit
  - Provided with personal vaporisers (9mg/ml nicotine), instructions for use
  - 30 day PP, CO verified

- **Smoking cessation clinic, Italy**
  - N = 34, unwilling to quit
  - Provided with EC, nicotine content tailored to match individual daily intake
  - Training programme and encouraged to quit
  - Cessation not defined

- **Smoking cessation clinic, Italy**
  - N = 34, unwilling to quit
  - Provided with EC, nicotine content tailored to match individual daily intake
  - Training programme and encouraged to quit
  - Cessation not defined
Ongoing studies

Of the 27 ongoing studies, 14 may contribute to future cessation meta-analyses (RCTs, measure cessation, 6m+ FU)