Electronic cigarettes for smoking cessation and reduction (Review)

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[Intervention Review]

Electronic cigarettes for smoking cessation and reduction

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ABSTRACT

Background

Electronic cigarettes (ECs) are electronic devices that heat a liquid - usually comprising propylene glycol and glycerol, with or without nicotine and flavours, stored in disposable or refillable cartridges or a reservoir - into an aerosol for inhalation. Since ECs appeared on the market in 2006 there has been a steady growth in sales. Smokers report using ECs to reduce risks of smoking, but some healthcare organisations have been reluctant to encourage smokers to switch to ECs, citing lack of evidence of efficacy and safety. Smokers, healthcare providers and regulators are interested to know if these devices can reduce the harms associated with smoking. In particular, healthcare providers have an urgent need to know what advice they should give to smokers enquiring about ECs.

Objectives

To examine the efficacy of ECs in helping people who smoke to achieve long-term abstinence; to examine the efficacy of ECs in helping people reduce cigarette consumption by at least 50% of baseline levels; and to assess the occurrence of adverse events associated with EC use.

Search methods

We searched the Cochrane Tobacco Addiction Groups Trials Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and two other databases for relevant records from 2004 to July 2014, together with reference checking and contact with study authors.

Selection criteria

We included randomized controlled trials (RCTs) in which current smokers (motivated or unmotivated to quit) were randomized to EC or a control condition, and which measured abstinence rates or changes in cigarette consumption at six months or longer. As the field of EC research is new, we also included cohort follow-up studies with at least six months follow-up. We included randomized cross-over trials and cohort follow-up studies that included at least one week of EC use for assessment of adverse events.

Data collection and analysis

One review author extracted data from the included studies and another checked them. Our main outcome measure was abstinence from smoking after at least six months follow-up, and we used the most rigorous definition available (continuous, biochemically validated, longest follow-up). For reduction we used a dichotomous approach (no change/reduction < 50% versus reduction by 50% or more of

baseline cigarette consumption). We used a fixed-effect Mantel-Haenszel model to calculate the risk ratio (RR) with a 95% confidence interval (CI) for each study, and where appropriate we pooled data from these studies in meta-analyses.

Main results

Our search identified almost 600 records, from which we include 29 representing 13 completed studies (two RCTs, 11 cohort). We identified nine ongoing trials. Two RCTs compared EC with placebo (non-nicotine) EC, with a combined sample size of 662 participants. One trial included minimal telephone support and one recruited smokers not intending to quit, and both used early EC models with low nicotine content. We judged the RCTs to be at low risk of bias, but under the GRADE system the overall quality of the evidence for our outcomes was rated 'low' or 'very low' because of imprecision due to the small number of trials. A 'low' grade means that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. A 'very low' grade means we are very uncertain about the estimate. Participants using an EC were more likely to have abstained from smoking for at least six months compared with participants using placebo EC (RR 2.29, 95% CI 1.05 to 4.96; placebo 4% versus EC 9%; 2 studies; GRADE: low). The one study that compared EC to nicotine patch found no significant difference in six-month abstinence rates, but the confidence intervals do not rule out a clinically important difference (RR 1.26, 95% CI: 0.68 to 2.34; GRADE: very low). A higher number of people were able to reduce cigarette consumption by at least half with ECs compared with placebo ECs (RR 1.31, 95% CI 1.02 to 1.68, 2 studies; placebo: 27% versus EC: 36%; GRADE: low) and compared with patch (RR 1.41, 95% CI 1.20 to 1.67, 1 study; patch: 44% versus EC: 61%; GRADE: very low). Unlike smoking cessation outcomes, reduction results were not biochemically verified.

None of the RCTs or cohort studies reported any serious adverse events (SAEs) that were considered to be plausibly related to EC use. One RCT provided data on the proportion of participants experiencing any adverse events. Although the proportion of participants in the study arms experiencing adverse events was similar, the confidence intervals are wide (ECs vs placebo EC RR 0.97, 95% CI 0.71 to 1.34; ECs vs patch RR 0.99, 95% CI 0.81 to 1.22). The other RCT reported no statistically significant difference in the frequency of AEs at three- or 12-month follow-up between the EC and placebo EC groups, and showed that in all groups the frequency of AEs (with the exception of throat irritation) decreased significantly over time.

Authors' conclusions

There is evidence from two trials that ECs help smokers to stop smoking long-term compared with placebo ECs. 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. The lack of difference between the effect of ECs compared with nicotine patches found in one trial is uncertain for similar reasons. ECs appear to help smokers unable to stop smoking altogether to reduce their cigarette consumption when compared with placebo ECs and nicotine patches, but the above limitations also affect certainty in this finding. In addition, lack of biochemical assessment of the actual reduction in smoke intake further limits this evidence. No evidence emerged that short-term EC use is associated with health risk.

PLAIN LANGUAGE SUMMARY

Can electronic cigarettes help people stop smoking or reduce the amount they smoke, and are they safe to use for this purpose?

Background

Electronic cigarettes (EC) are electronic devices that produce a smoke-like aerosol (commonly referred to as vapour) that the user inhales. This vapour typically contains nicotine without most of the toxins smokers inhale with cigarette smoke. ECs have become popular with smokers who want to reduce the risks of smoking. This review aimed to find out whether ECs help smokers stop or cut down on their smoking, and whether it is safe to use ECs to do this.

Study characteristics

We searched for trials published up to July 2014 and found 13 that help answer these questions. Two of the trials compared ECs with and without nicotine. These studies were judged to be at low risk of bias. They were conducted in New Zealand and Italy, and measured whether people had quit smoking for at least six months. In one study, people wanted to quit smoking, but in the other study, they did not. The trial in people who wanted to quit smoking also compared ECs to nicotine patches. The rest of the studies did not put people into treatment groups so could not directly compare ECs with something else. These studies can tell us less about how ECs might help with quitting smoking or with cutting down.

Key results

Combined results from two studies, involving over 600 people, showed that using an EC containing nicotine increased the chances of stopping smoking long-term compared to using an EC without nicotine. Using an EC with nicotine also helped more smokers reduce the amount they smoked by at least half compared to using an EC without nicotine. We could not determine if EC was better than a nicotine patch in helping people stop smoking because the number of participants in the study was low. More studies are needed to evaluate this effect. This study showed that people who used EC were more likely to cut down the amount they smoked by at least half than people using a patch. The other studies were of lower quality, but they supported these findings. There was no evidence that using EC at the same time as using regular cigarettes made people less likely to quit smoking. None of the studies found that smokers who used EC short-term (for 2 years or less) had an increased health risk compared to smokers who did not use EC.

Quality of the evidence

The quality of the evidence overall is low because it is based on only a small number of studies. More studies of EC are needed. Some are already underway.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Electronic cigarettes (EC) for smoking cessation and reduction

Patient or population: people defined as current smokers at enrolment into trials, motivated or unmotivated to quit
Intervention: nicotine-containing electronic cigarettes
Comparison: placebo electronic cigarettes or nicotine replacement therapy

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk[1]	Corresponding risk				
	Control	Electronic cigarettes				
Cessation: Nicotine EC versus placebo EC[2] assessed with exhaled CO Follow-up: 6 - 12 months	**40 per 1000**	**93 per 1000** (42 to 201)	**RR 2.29** (1.05 to 4.96)	662 (2 studies)	⊕⊕◯◯ **low**[3,4]	Only RCTs reported here. Some cohort data also available (see full review) but only RCTs provide efficacy data
Cessation: Nicotine EC versus nicotine replacement therapy assessed with exhaled CO Follow-up: 6 months	**58 per 1000**	**73 per 1000** (39 to 135)	**RR 1.26** (0.68 to 2.34)	584 (1 study)	⊕◯◯◯ **very low**[3,5]	As above
Reduction: Nicotine EC versus placebo EC proportion of participants who achieved ≥ 50% reduction in baseline cigarette consumption Follow-up: 6 - 12 months	**271 per 1000**	**355 per 1000** (277 to 455)	**RR 1.31** (1.02 to 1.68)	612 (2 studies)	⊕⊕◯◯ **low**[3,4]	As above. Analysis excludes quitters

Reduction: Nicotine EC versus nicotine replacement therapy proportion of participants who achieved ≥ 50% reduction in baseline cigarette consumption Follow-up: 6 months	**435 per 1000**	**614 per 1000** (522 to 727)	**RR 1.41** (1.20 to 1.67)	546 (1 study)	⊕○○○ **very low**[3,5]	As above. Analysis excludes quitters
Adverse events (AEs) Follow-up: 6 - 12 months	Summary data not available. None of the studies 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			1090 (8 studies (2 RCTs, 6 cohort))	⊕⊕○○ **low**[6,7]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] 'Assumed risk' calculated as risk in control groups.
[2] 'Placebo EC' refers to ECs which do not contain nicotine.
[3] Downgraded one level due to indirectness. The electronic cigarette used in Bullen 2013 was not very effective at delivering nicotine
[4] Downgraded one level due to imprecision. Only two included studies, small number of events (<300) in each arm
[5] Downgraded two levels due to imprecision. Only one included study, with small number of events in each arm
[6] Downgraded due to risk of bias. 6/8 included studies (cohort studies) judged to be at high risk of bias
[7] Downgraded due to imprecision. Only one trial provided data for nicotine EC versus nicotine replacement therapy

BACKGROUND

Throughout this review, we discuss two types of cigarettes: electronic and conventional tobacco cigarettes. To avoid confusion, all mention of smoking, smoking cessation, cigarette use, smoke intake, etc., concern conventional cigarettes. When the text concerns electronic cigarettes we use the abbreviation 'EC'. EC users are sometimes described as vapers, and EC use as vaping. We refer to ECs that do not contain nicotine as placebo ECs.

Description of the condition

Stopping smoking is associated with large health benefits. Despite most smokers wanting to quit, few manage to succeed in the long term. Almost half who try to quit without support will not manage to stop for even a week, and fewer than 5% remain abstinent at one year after quitting (Hughes 2004).

Behavioural support and medications such as patches or gum increase the chances of quitting, but even with this additional support long-term quit rates remain low (Cahill 2012; Hughes 2014; Lancaster 2005; Stead 2005; Stead 2006; Stead 2012). One of the limitations of current treatments is that none adequately addresses the sensory and behavioural aspects of smoking that smokers miss when they stop smoking (e.g., holding a cigarette in their hands, taking a puff, etc.). ECs may offer a way to overcome this limitation.

There is no doubt that people become dependent on tobacco, and find it difficult to stop smoking, primarily because of nicotine and its actions on the brain's reward system (Balfour 2004). However, other factors also contribute to tobacco dependence (Rose 2006). Sensory and behavioural cues appear to provide additional reinforcement of smoking behaviour (Rose 1993; Rose 2000) and over time become almost as rewarding as nicotine. There are several lines of evidence to support this. Firstly, smokers appear to have a preference for cigarette smoke compared to other forms of nicotine delivery. This is partly related to its speed of nicotine delivery. However, even when nicotine is administered intravenously it does not provide the same level of satisfaction or reward as smoking (Rose 2000; Westman 1996). Secondly, the local sensory effects of smoking (e.g., the 'scratch' in the back of the throat) may be important for enjoyment and reward. Numbing the sensations of cigarette smoke by anaesthetising the upper and lower respiratory tract leads to less enjoyment of smoking (Rose 1985). Conversely, products that mimic the sensory effects of smoking on the mouth and throat (such as citric acid, black pepper, and ascorbic acid) reduce craving and some withdrawal symptoms, at least in the short term (Rose 1994; Levin 1993; Westman 1995). Thirdly, de-nicotinised cigarettes (DNCs), which have a very low content of nicotine (e.g. 0.08 mg instead of the normal 1 mg) and so have negligible or no central effects, have also been investigated for their role in aiding smoking cessation (Przulj 2013). Despite not delivering nicotine, DNCs are satisfying over the initial few days of abstinence from nicotine (Donny 2007; Pickworth 1999; Rose 2000). They also reduce tobacco withdrawal symptoms, including urges to smoke and low mood (Barrett 2010; Donny 2009; Perkins 2010; Rose 2000), and have been shown to improve long-term continuous abstinence rates in one study (Walker 2012).

An ideal candidate for a smoking cessation product would not only help relieve the unpleasant effects of nicotine withdrawal but would also be an effective substitute for smoking behaviour and the rituals and sensations that accompany smoking, but without the health risks associated with the inhalation of tobacco smoke. The only pharmaceutical treatment available that has some of these characteristics is the nicotine inhalator. However, the inhalator does not have greater cessation efficacy than the other nicotine replacement therapy (NRT) products (Hajek 1999; Stead 2012). This may in part be due to the considerable effort (e.g., 20 minutes of continuous puffing) needed to provide nicotine blood concentrations consistent with other NRTs (Schneider 2001). Adherence to correct use of the inhalator is low compared to other NRTs (Hajek 1999). It is therefore possible that any advantage of sensorimotor replacement is diminished by low nicotine delivery and limited similarities between inhalator use and sensations of smoking (Bullen 2010).

Description of the intervention

ECs are electronic vaporising devices broadly similar in appearance to cigarettes, cigars or pipes, although many newer products are quite different in appearance to cigarettes or cigars. All have in common the ability to heat a liquid - usually comprising propylene glycol and glycerol, with or without nicotine and flavours, and stored in disposable or refillable cartridges or a reservoir - into an aerosol for inhalation. The commonly used term for this aerosol is vapour, which we use throughout the review. ECs are currently being promoted by retailers to use instead of cigarettes when in smoke-free environments, and to replace conventional cigarettes with a safer alternative.

ECs provide sensations similar to smoking a cigarette. They provide taste and throat sensations that are closer to smoking than those provided by the nicotine inhalator (Barbeau 2013). The vapour that looks like tobacco smoke is only visible when the user exhales after drawing on the mouthpiece, not when the device is being held.

There are hundreds of different brands and models of EC available that differ in the composition of the fluid in the cartridge or in the EC reservoir (nicotine content, flavours and other components) (Goniewicz 2012; Goniewicz 2014). This makes a blanket assessment of cessation efficacy difficult. Conclusions should relate to the particular type of EC tested and the composition of the liquid being aerosolised.

Initial studies showed that the brands of EC tested delivered very low amounts of nicotine to naive users (Bullen 2010; Eissenberg 2010; Vansickel 2010). However, the studies suggested that even

in the absence of good nicotine delivery, these brands of EC could alleviate urges to smoke. One study allowed a comparison of EC and inhalator, although its main objective was a comparison of ECs with and without nicotine. Puffing for 20 minutes on the inhalator and puffing for five minutes on the EC had similar effects on desire to smoke after overnight abstinence (Bullen 2010). Later studies that have measured nicotine pharmacokinetics in both experienced (Vansickel 2013) and naive (Vansickel 2012) EC users have found that some EC users can achieve blood nicotine levels similar to those achieved with smoking.

Throughout this review we refer to a nicotine-containing EC as 'nicotine EC' and to a nicotine-free EC as 'placebo EC'. The 'placebo' comparison is a test just of the nicotine effect and not of the potential sensorimotor replacement that the EC may provide.

Why it is important to do this review

Since ECs appeared on the market in 2006 there has been a steady growth in sales, with some commentators reporting that ECs are a threat to the sales of cigarettes (Herzog 2013). This growth in sales is reflected in population survey data that show an increased awareness and use of ECs over time (ASH 2014; Agaku 2014; Ayers 2011; Brown 2014b; Gallus 2014). ECs are used almost exclusively by smokers or ex-smokers (ASH 2014; Douptcheva 2013; West 2014). A small proportion of never-smokers have reported trying or experimenting with ECs but they do not seem to progress to regular or even daily use (CDC 2013; West 2014). Of smokers who try ECs, fewer than 15% become daily users (Douptcheva 2013; Kralikova 2012), which suggests that ECs are still not an entirely satisfying replacement for smoking.

Smokers report using ECs to help them stop or reduce smoking, but various health organisations have been reluctant to support the use of ECs. Some have supported bans on EC sales (e.g., Bam 2014) and others have recommended that ECs should be regulated as tobacco products but with lower nicotine content (e.g., European Parliament 2014) or be submitted to strict medicinal regulation (e.g., MHRA 2014). This would make them more highly regulated than tobacco products and would reduce their competitiveness against cigarettes. There is now general agreement that EC use exposes the user to fewer toxicants than smoking tobacco cigarettes. However, those public health experts calling for ECs to be stringently regulated (e.g., Grana 2014a; WHO 2014) cite the lack of quality control measures, possible harms of second-hand EC vapour inhalation, concerns that the products may be a gateway to smoking initiation, concerns that ECs may undermine smoke-free legislation if used in smoke-free spaces, and concerns regarding the involvement of the tobacco industry. However, other reviews of available data do not support these concerns (Farsalinos 2014; Hajek 2014; McNeill 2014).

Regarding safety, categorical statements about the toxicity of ECs are not possible because of the large number of devices and fluids available and the frequent addition of new products to the market. However, among those brands of EC that have been tested, levels of toxins have been found to be substantially lower than in cigarettes, and are present at levels that are unlikely to represent a significant risk to health to either the user or to bystanders (Hajek 2014). Short- to medium-term use of ECs is associated with few adverse events (Bullen 2013; Caponnetto 2013a). Long-term effects beyond 12 months are unknown, and although these may emerge in due course, it is highly likely that, based on what is known about liquid and vapour constituents and patterns of use, there will be few risks, and fewer adverse health effects than from ongoing smoking.

Smokers, healthcare providers and regulators are interested to know if these devices can reduce the harms associated with smoking. In particular, healthcare providers have an urgent need to know what advice they should give to people who smoke. The largest health gains are achieved from stopping smoking completely, as opposed to reducing cigarette consumption, and as such the primary objective of this review is to determine the effectiveness of ECs in aiding smoking cessation. However, there is also an opportunity to investigate if the EC has potential to aid reduction in cigarette consumption in those smokers who cannot or do not want to stop smoking altogether. NRT, when used in people who are not ready to quit, has been found to approximately double the odds of achieving at least a 50% reduction in daily cigarette consumption compared to placebo, although this was not fully matched by reductions in markers of tobacco exposure (Stead 2007). Thus, some uncertainty about the health benefits of this approach remains. Nevertheless, support is growing for the use of NRT to aid cigarette reduction, especially in the context of preparing smokers for quitting (Stead 2007). The UK National Institute for Health and Care Excellence also recommends harm reduction approaches for people who may want to stop smoking without giving up nicotine or for those that just want to reduce their cigarette consumption (NICE 2013). These approaches include temporary or long-term use of nicotine-containing products, although only those products that are currently licensed (Kelly 2014). This review will therefore also evaluate the efficacy of ECs to reduce cigarette use with a corresponding decrease in biochemical markers of tobacco exposure, where such data are available.

OBJECTIVES

The main objective is to evaluate the efficacy of electronic cigarettes (ECs) for helping people who smoke to achieve long-term abstinence.

The secondary objectives are: 1) to evaluate the efficacy of ECs for helping smokers to reduce cigarette consumption by at least 50% of baseline levels; and 2) to assess the occurrence of adverse events associated with EC use.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) in which smokers are randomized to ECs or to a control condition, and which measure abstinence rates or changes in cigarette consumption at six months or longer, to determine the efficacy of ECs in aiding smoking cessation and reduction. We anticipated that the search would return few RCTs and so we also considered the results from cohort follow-up studies with six months' or longer follow-up.

We included randomized cross-over trials and cohort follow-up studies with follow-up of greater than a week, for assessment of adverse events.

We included studies regardless of their publication status or language of publication.

Types of participants

People defined as current smokers at enrolment into the trial. Participants can be motivated or unmotivated to quit.

Types of interventions

We compare ECs with placebo ECs, ECs versus alternative smoking cessation aids, including NRT or no intervention, and ECs added to standard smoking cessation treatment (behavioural or pharmacological or both) with standard treatment alone.

Types of outcome measures

Primary outcomes

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 where reported.

Secondary outcomes

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.

We collected any data on adverse events at one week or longer, serious and non-serious, from the included studies.

Search methods for identification of studies

Electronic searches

We searched the following databases in July 2014:

- Cochrane Tobacco Addiction Group Specialised Register
- Cochrane Central Register of Controlled Trials

(CENTRAL) (*The Cochrane Library*, Issue 7, 2014)

- MEDLINE (OVID SP) (2004 to July 2014)
- EMBASE (OVID SP) (2004 to July 2014)
- PsycINFO (OVID SP) (2004 to July 2014)
- CINAHL (EBSCO Host) (2004 to July 2014)

The search terms were broad and included e-cig$ OR elect$ cigar$ OR electronic nicotine. The search strategy for MEDLINE (Ovid SP) is shown in Appendix 1.

The search date parameters are limited to 2004 to the present, due to the fact that ECs were not available before 2004.

Searching other resources

We searched the reference lists of studies found in the literature search and the metaRegister of controlled trials database (www.isrctn.com/page/mrct). We also contacted authors of known trials and other published EC studies.

Data collection and analysis

Selection of studies

Two review authors (HM and JHB) independently prescreened all titles and abstracts obtained from the search, using a screening checklist. Where there was disagreement, we obtained the full-text version and resolved the disagreement by discussion with a third review author (PH).

Full text versions of the potentially relevant papers were obtained and independently screened for inclusion by two reviewers (HM and JHB). Any disagreement was resolved with a third reviewer (PH).

Data extraction and management

Two review authors (HM or JHB) extracted data from the included studies, and checked them against each other. A third review author (PH) was available to review and resolve any discrepancies. We extracted data on:

- Author
- Date and place of publication
- Study design
- Inclusion and exclusion criteria
- Setting
- Summary of study participant characteristics

- Summary of intervention and control conditions
- Number of participants in each arm
- Smoking cessation outcomes
- Cigarette use per day
- Type of biochemical validation (if any)
- Adverse events (AEs) and serious adverse events (SAEs)
- Assessment time points
- Risk of bias in the domains specified below
- Additional comments

We adopted a broad focus to detect a variety of adverse events. One review author then entered the data into Review Manager 5 software for analyses, and another checked them.

Assessment of risk of bias in included studies

Two review authors (HM and JHB) independently assessed the risk of bias for each included study, following the approach recommended in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). This approach uses a domain-based evaluation that addresses seven different areas: random sequence generation; allocation concealment; blinding of participants and providers; blinding of outcome assessment; incomplete outcome data; selective outcome reporting; and other potential sources of bias. We assigned a grade (low, high, or unclear) for risk of bias for each domain. We resolved disagreements by discussion with a third author (PH).

Measures of treatment effect

We analysed dichotomous data by calculating the risk ratio (RR), using the longest follow-up data reported. We have used a dichotomous approach for cessation, change in cigarette consumption (no change/reduction < 50% versus reduction by 50% or more) and carbon monoxide (CO) in expired breath where this was possible, using the cut-offs employed in the original study reports. For cessation and reduction of 50% or more, we calculated the RR as ((number of events in intervention condition/intervention denominator) / (number of events in control condition/control denominator)) with a 95% confidence interval.
We analysed continuous data (other measures of tobacco exposure) by comparing the difference between the mean change from baseline to the longest follow-up point in the intervention and control groups.

Unit of analysis issues

We extracted data on smoking outcomes only from RCTs in which individuals were the unit of randomisation. In the case of trials with multiple arms, we combined all relevant experimental intervention groups of the study into a single group, and combined all relevant control intervention groups into a single control group.
We offer a narrative synthesis of data from cohort studies.

Dealing with missing data

We used a conservative approach for the treatment of missing data for smoking outcomes. For smoking cessation, we treated participants with missing data as still smoking. For smoking reduction, we treated participants with missing data as having experienced no reduction in cigarettes smoked per day. We based the proportion of people affected by adverse events on the number of people available for follow-up, and not the number randomized.

Assessment of heterogeneity

We assessed the clinical and methodological diversity between studies to guide our decision as to whether data should be pooled. We were also guided by the degree of statistical heterogeneity, assessed by calculating the I^2 statistic (Higgins 2003): we considered a value greater than 50% as evidence of substantial heterogeneity.

Assessment of reporting biases

Reporting bias is best assessed using funnel plots, where 10 or more RCTs contribute to an outcome. However, there are currently insufficient studies to support this approach.

Data synthesis

We provide a narrative summary of the included studies. Where appropriate, we have pooled data from these studies in meta-analyses. For dichotomous data, we used a fixed-effect Mantel-Haenszel model to calculate the risk ratio with a 95% confidence interval. We had planned to use a random-effects model if there was substantial heterogeneity, but this was not necessary.
We had planned to calculate the summary estimates for continuous outcomes (e.g. biomarkers of tobacco exposure and cigarettes per day (CPD)) using the inverse variance approach (also with a 95% CI). However, there were insufficient data with which to do so.
For adverse events, we originally planned to enter the most commonly-reported adverse events into meta-analyses to determine if there were any significant differences between the EC and control groups. We also originally planned to include data from cross-over trials in a meta-analysis using paired data obtained from reports. However, there were again insufficient data with which to do so, and hence we have summarised adverse event data narratively.

Subgroup analysis and investigation of heterogeneity

We had planned to undertake subgroup analyses to investigate differences between studies, such as:

- Intensity of behavioural support used;
- Type of control group (e.g., placebo EC, nicotine NRT);
- Type of participants (e.g. experience of EC use).

However, there were too few studies to conduct such analyses. Should further studies become available in future, we will follow this approach.

Sensitivity analysis

We had planned to undertake sensitivity analyses to assess the effect of removing studies judged to be at high risk of bias. However, there were too few studies to conduct such analyses. Should further studies become available in subsequent updates, we will adopt this approach.

Summary of findings table

Following standard Cochrane methodology, we created a 'Summary of findings' table for each of the three outcomes. For cessation and reduction outcomes, the 'Summary of findings' table only includes data from randomized controlled trials. Also following standard Cochrane methodology, we used the five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome, and to draw conclusions about the quality of evidence within the text of the review.

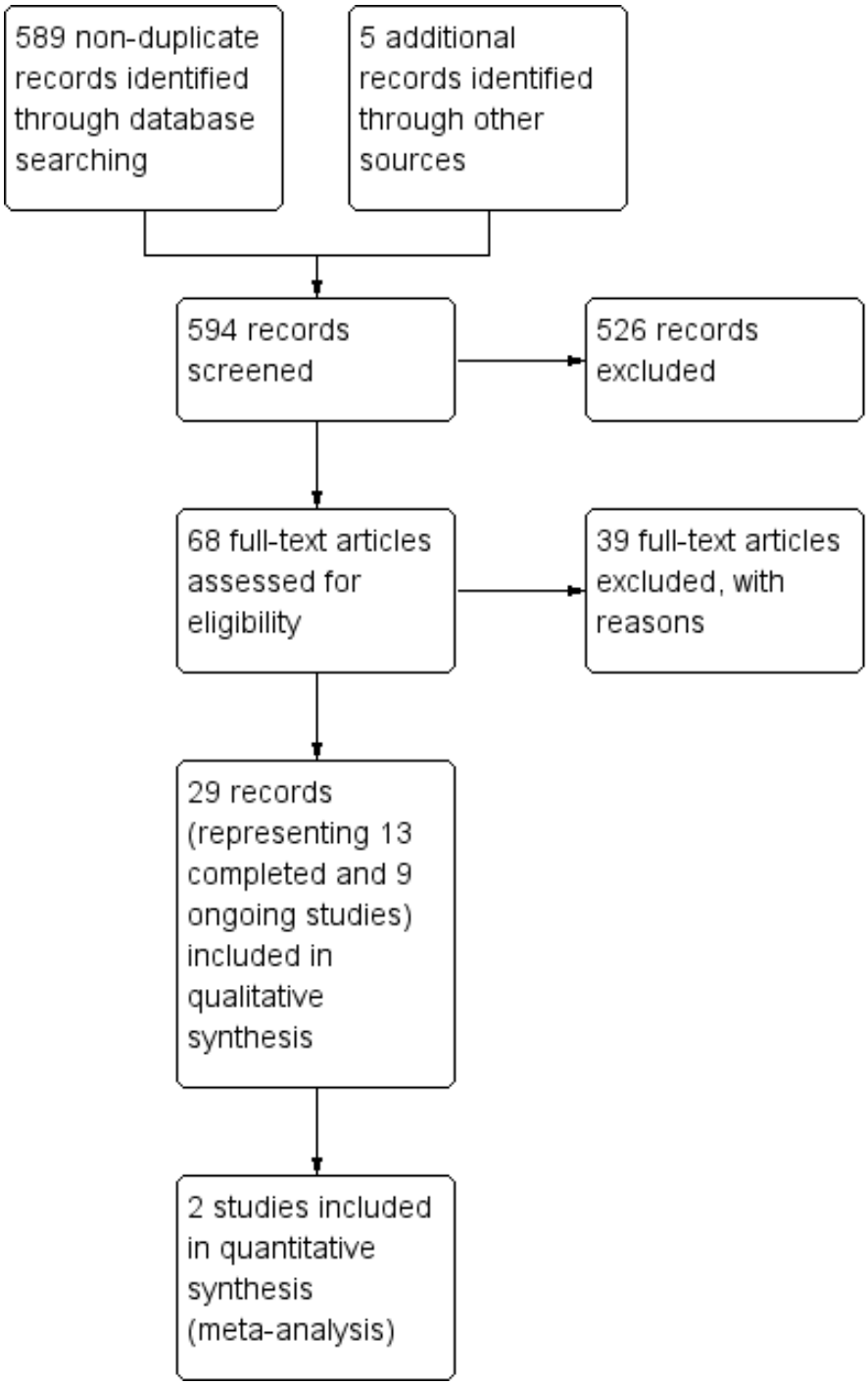
RESULTS

Description of studies

Results of the search

Our search identified 589 non-duplicate records. We found a further five records through screening references in the papers identified through electronic searches. We screened all records and retrieved the full-text papers of 68 potentially relevant studies. Two were conference abstracts and we contacted the authors for the full-text documents. We excluded 39 papers after full-text screening, leaving 29 records representing 13 completed studies (18 records) and nine ongoing trials (11 records), included in this review (see Figure 1, the Characteristics of included studies table, and the Characteristics of excluded studies table). The completed studies include two RCTs and 10 prospective cohort studies that describe changes in smoking behaviour over time or adverse events (AEs), or both. In one of the included studies (Choi 2014), the data come from authors' response to a criticism of their paper - the data were not included in the original study report. One study (Polosa 2014) provided data on changes in respiratory parameters and symptoms in people with asthma that were using electronic cigarettes (ECs). Although this used a retrospective design it used data from different time points and used routine clinical records that we think are adequate for capturing data concerning reduction and adverse events.

Figure 1. Study flow diagram.



Included studies

The key features of the included studies are summarised by study type below. Further details on each included study can be found in the Characteristics of included studies table.

Randomized controlled trials

We identified only two completed randomized controlled trials (Bullen 2013; Caponnetto 2013a).

The ASCEND trial (Bullen 2013) randomized 657 smokers (middle-aged, highly dependent, with one-third being of New Zealand Maori origin) who wanted to quit to use either an Elusion brand EC (first generation technology) with cartridges containing 16 mg nicotine, or 21 mg/24-hour 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, which is standard practice in New Zealand, but also received a voucher to cover the dispensing costs. 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. This was determined in a subsample of four participants, who had used the EC for at least one week, volunteered to give a baseline blood sample, and then use their EC, taking one puff every minute over 10 minutes. They then provided five further blood samples at approximately 10, 20, 30, and 60 minutes after the start of EC use. Pharmacokinetic analyses showed that plasma nicotine concentrations peaked (a median increase of 2.1 ng/ml from baseline) at 10 minutes after the start of EC use. Participants were followed up at six months post-TQD and self-reported abstinence was validated by carbon monoxide (CO) in expired breath, in line with the Russell Standard (West 2005). Participants who were still smoking at follow-up were asked to report their daily cigarette consumption, and a change from baseline consumption was measured.

In the three-arm ECLAT trial (Caponnetto 2013a), 300 smokers (again middle-aged and highly dependent) who were not intending to quit smoking in the next 30 days were randomized to use a 'Categoria' brand EC (model 401, which is no longer produced) 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. The EC was presented simply as a healthier alternative to tobacco smoke, and could be freely used ad libitum (up to four cartridges per day) as a tobacco substitute. Participants were seen on eight occasions over 12 months, once at baseline and at seven follow-up visits where they received more cartridges, handed in smoking diaries, and had CO and vital signs measured. Abstinence at 12 months was defined as complete self-reported abstinence from tobacco smoking since the previous visit at six months, confirmed with CO less than 7 parts per million (ppm) at six and 12 months. Participants who were still smoking at follow-up were asked to report their daily cigarette consumption, and a change from baseline consumption was measured.

Prospective cohort studies: smoking behaviour

Three prospective intervention studies described changes in smoking behaviour in smokers provided with ECs to reduce or stop smoking. Three other studies described changes in smoking status in smokers who had tried or used ECs in the past.

The first of the three intervention studies recruited 14 smokers with schizophrenia from among inpatients at a psychiatric institution in Italy (Caponnetto 2013b). All had been smoking at least 20 cigarettes per day for at least the past 10 years and were not intending to quit. Participants were seen at baseline and provided with an EC ('Categoria' brand) with an initial four-week supply of 7.4 mg nicotine cartridges. They were instructed to use their EC ad libitum (up to four cartridges per day), but no instruction on cessation or reduction was provided. Follow-up was completed at 1, 2, 3, 6 and 12 months when cigarette consumption, CO, AEs and positive and negative symptoms of schizophrenia were measured. Further EC cartridges were supplied at one, two, and three months.

Another similarly designed study examined the effects of EC use over an extended period of time in 40 highly dependent middle-aged smokers not wanting to quit smoking at any time in the next 30 days, recruited from among staff working in an Italian hospital (Polosa 2011). At baseline they were given an EC ('Categoria' brand) with a four-week supply of 7.4 mg nicotine cartridges and instructed to use ad libitum (up to four cartridges per day). No instruction on cessation or reduction was provided. Participants were followed up at 1, 2, 3, 6, 18 and 24 months, when cigarette consumption, CO, and AEs were recorded. Additional EC cartridges could be requested at months one, two, and three.

The third study (Ely 2013) recruited 48 smokers, who wanted to quit or switch from cigarettes to ECs, from among 640 patients of a single family medical practice in Colorado (USA) who were recorded as current smokers. The intervention was based on the '5 As' and the transtheoretical model, and participants were informed of the range of treatment options at the start of the programme. They were provided with written information on 'blu cig' and 'smoke tip' ECs, regarding cost, availability, and nicotine dosage options. All participants used an EC, with 16 using bupropion and two using varenicline as well. Follow-up was undertaken by telephone at two weeks, one, three and six months after the start of the intervention. No definition of abstinence was provided, nor

were self reports biochemically verified.

The first of the non-intervention studies (Etter 2014) followed up smokers and EC users accessing web sites selling or informing users about EC and online EC forums. The survey was open to all nationalities with 34% of respondents from the USA, 24% from France, 8% from the UK, 6% from Switzerland, and 28% from other countries. Three hundred and sixty-seven participants who had completed a baseline questionnaire also completed a follow-up survey one year later when they were asked to provide follow-up data on EC use and smoking behaviour. Of these participants, 35 (10%) were occasional or daily smokers and daily EC users at baseline.

In another longitudinal web-based survey, Grana 2014b recruited 949 current cigarette smokers (59% smoked within 30 minutes of waking and 69% never expected to quit or did not intend to quit in the next six months) who completed surveys at both baseline and one-year follow-up. At baseline 9% (n = 88) were using ECs (defined as use in the past 30 days). No data on the nicotine content of the EC were provided. Self-reported abstinence (not defined) was measured at one-year follow-up.

In a response to a letter criticising their main paper, which did not provide data on EC users and smoking outcomes, Choi 2014 presented new data from a prospective cohort study of young adults recruited from Midwestern states of the USA. The letter reports on smoking cessation outcomes (not defined) in a sample of smokers who used ECs for one or more days in last 30 days at baseline (no N given), comparing these to a sample of baseline smokers who had never used ECs at baseline. No data on the nicotine content of the EC were provided. The main paper included 1379 participants (mean age 24) who had never used ECs, 17.8% of whom were reported to be current smokers.

Although not a prospective cohort study, Polosa 2014 allowed for extraction of data regarding reduction in cigarette consumption. This study identified 18 participants with mild to moderate asthma who had previously smoked an average of 22 cigarettes per day, who reported regular EC use on at least two consecutive follow-up visits, approximately six months apart, using a retrospective audit of clinical records from a respiratory outpatient clinic in Italy from September 2012 until December 2013. Ten were using ECs only, and eight used ECs and smoked up to five cigarettes per day. The duration of EC use ranged from 10 to 14 months, with 12 participants using them for more than a year. All started on first-generation ECs, but the 'majority' switched to a 'personal vaporiser' (second or third generation). The authors collected data from four clinic visits: pre-baseline (6 to 12 months prior to baseline); baseline visit (pre-EC use), which occurred approximately six months prior to the first follow-up visit; six-month follow-up; and 12-month follow-up.

Prospective cohort studies: adverse event data only

We include five short-term cohort studies that report on adverse events. These studies are not included in smoking analyses due to short follow-up.

Humair 2014 describes a prospective cohort study involving 17 participants (all highly dependent smokers, 82% with a mental illness), recruited from a university hospital outpatient clinic in Switzerland, who chose to use an EC to help them stop or reduce smoking. NRT or varenicline were used at some stage by 59% of participants in addition to EC.

McRobbie 2014 recruited 40 daily smokers who wanted to quit, from advertisements placed in free London newspapers. Participants attended a baseline session one week prior to their TQD. On the TQD, participants were provided with ECs ('Green Smoke', first-generation device, 2.4% nicotine cartridges). Two cartridges per day were supplied initially, with the supply later adjusted to actual use. Participants attended weekly follow-up sessions for four weeks, and received standard behavioural support. Cigarette consumption and CO readings collected at each session and urine samples for cotinine and 3-HPMA analysis were collected at baseline and at four weeks post-TQD.

Nides 2014 recruited 29 smokers in good health and not intending to reduce or quit smoking in the next 30 days. The aim of this study was to investigate nicotine delivery and potential for smoking reduction or cessation. Participants were provided with a 10-day supply of disposable electronic cigarette ('NJOY King Bold' brand containing 26 mg of nicotine) and instructed to use them ad libitum for a week. At the end of the week, 25 participants returned to the clinic, after abstaining from smoking and EC use for 12 hour. They undertook two series, an hour apart, of 10 puffs on their EC, and changes in plasma nicotine, heart rate and CO, and withdrawal symptoms were measured. Adverse events that occurred during the period of ad libitum use were also collected.

Polosa 2014, described above, also provided data on changes in respiratory function. At each visit, participants were assessed by clinical history and examination, and by re-evaluation of treatment adherence and efficacy. Information was gathered on asthma control (using Juniper's Asthma Control Questionnaire), the number of exacerbations from the previous follow-up visit (defined as an increase in respiratory symptoms requiring a short course of oral or parenteral corticosteroids), spirometry measurements including FEV1, FVC, FEV1/FVC, forced expiratory flow at the middle half of the FVC (FEF 25% - 75%), and bronchial provocation tests assessing Airway Hyper Responsiveness (AHR) with methacholine (some participants only).

Van Staden 2013 recruited 15 healthy smokers of at least 10 cigarettes per day from a military hospital in South Africa. They were each provided with an EC ('Twisp eGo' 18 mg/ml nicotine) and asked to use this and to stop smoking for two weeks. Blood pressure, pulse, arterial and venous COHb and blood oxygen saturation were measured at baseline and two-week follow-up in 13 participants that attended both sessions.

Excluded studies

The reasons for exclusion of the 39 studies that we reviewed are briefly summarised below, but further detail can be found in the Excluded studies table.

The majority of excluded studies were ruled out because the participants used ECs for less than a week, or the study report contained no information on cessation, reduction or adverse events. In these cases we were unable to determine if the excluded studies intended to measure these outcomes. As per the protocol, we excluded cross-sectional studies with data collected at one time point only for reasons including inability to control for confounding variables, problems with the definition of EC use (e.g. any use in the last 30 days), and recall bias.

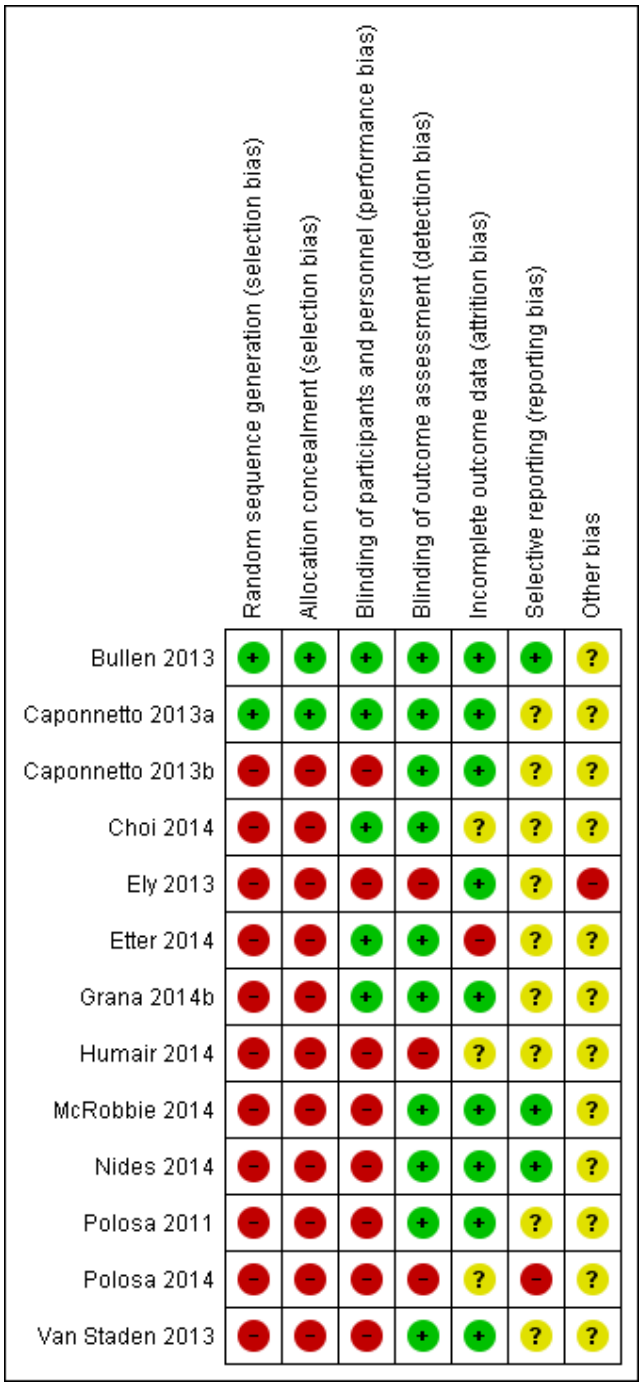
Risk of bias in included studies

The risk of bias in the two RCTs (Bullen 2013; Caponnetto 2013a) was low across all domains. The only exception was in the reporting bias in Caponnetto 2013a, as it was unclear if the original intention was to combine the two nicotine-containing EC groups or not. In the sample size calculation the authors compared the nicotine EC group with the placebo EC, but results are not reported in this way. In both studies the randomization procedures were adequate, biochemical validation of abstinence was used, and an intention-to-treat analysis was undertaken where all participants lost to follow-up were considered to be smoking. The lost-to-follow-up (LTFU) rate in Bullen 2013 was 22%. Although the patch group had a higher LTFU and withdrawal than the EC group (patch: 27%; nicotine-EC: 16%; placebo EC 22%), there was minimal difference between the per-protocol and ITT analyses and so attrition bias was deemed to be at low risk. LTFU rates were similar among the three arms at 12 months in Caponnetto 2013a (35% in 7.2 mg nicotine group; 37% in 5.4 mg nicotine group; 45% in no-nicotine group). Reduction data are self-reported only.

All other included studies, by nature of design, were categorised as being at high risk of selection bias. The three surveys (Choi 2014; Etter 2014; Grana 2014b) did not validate self-reported abstinence, excluded EC users who stopped smoking, and in case of Grana 2014b and Choi 2014, 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. Five cohort studies (Caponnetto 2013b; McRobbie 2014; Nides 2014; Polosa 2011; Van Staden 2013) included biochemical validation of participants and so were graded as being at low risk of detection bias. Rates of follow-up were mixed in the non-randomized studies. Caponnetto 2013b followed up all participants. Etter 2014 had one-year data from only 367 (28%) of the 1329 people that completed the baseline survey. For many of the cohort studies we were unable to determine prespecified outcomes and hence rated these as being at unclear risk of reporting bias. Finally, Ely 2013 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. This study was therefore judged as being at high risk of other bias.

Details of risk of bias judgements for each domain of each included study can be found in the Characteristics of included studies table. Figure 2 illustrates judgements for each included study.

Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Effects of interventions

See: **Summary of findings for the main comparison** Electronic cigarettes for smoking cessation and reduction

In this section we have summarised the effects of ECs on smoking cessation, reduction and adverse events.

Cessation

Randomized controlled trials

In the trial comparing EC to patch (Bullen 2013) there was no significant difference in six-month CO-validated continuous abstinence between the treatment arms (7.3%, 5.8% and 4.1%, in the nicotine EC, patch and placebo EC arms respectively). We made two comparisons. The first compares abstinence rates between nicotine and placebo EC (7.3% vs. 4.1%, risk ratio (RR) 1.77, 95% confidence interval (CI): 0.54 to 5.77, Analysis 1.1). The second compares abstinence rates between the nicotine EC and patch arms; our analysis does not show a significant difference between the two (7.3% vs. 5.8%, RR 1.26, 95% CI 0.68 to 2.34, Analysis 1.2). Fewer than half of all participants across all groups accessed support (39.8%, 35.9%, and 35.6% in the nicotine EC, patch and placebo EC arms respectively).

In the other RCT (Caponnetto 2013a) one-year abstinence rates (at least six months of not smoking and CO-validated) were higher in the two nicotine EC arms (13% and 9%) compared with the placebo EC group (4%). In our analysis we combined the two nicotine EC arms and compared these with the placebo group. The difference was not statistically significant (11% vs. 4%, RR 2.75, 95% CI 0.97 to 7.76, Analysis 1.1).

We combined data from the two studies comparing abstinence rates in nicotine versus placebo EC groups. There was no significant statistical heterogeneity between the studies (Chi^2 = 0.30, P = 0.58; I^2 = 0%) and pooled results showed use of a nicotine-containing EC was associated with higher abstinence rates than placebo EC use (RR 2.29, 95% CI 1.05 to 4.96, Analysis 1.1; 662 participants).

Cohort studies

The abstinence rates from each cohort study are summarised in Table 1.

Among the intervention cohort studies that enrolled smokers unmotivated to quit, Polosa 2011 reported abstinence rates (30 day point prevalence, CO-validated abstinence) of 22.5% at six months and 12.5% at two years. In the study of highly dependent smokers with schizophrenia, 14% (2/14) achieved abstinence (CO-validated) at one year (Caponnetto 2013b). In Ely 2013, 43.8% (21/48) of participants were abstinent from smoking at the completion of the six-month programme. Of those that exclusively used ECs (n = 26), 50% (13) were abstinent, compared with 37.5% (6/16) of those who used both ECs and bupropion and 100% (2/2) who used ECs with varenicline.

The longitudinal surveys contained relatively few smokers who were using ECs at baseline. Etter 2014 showed one-year self-reported abstinence rates of 45.7% (16/35) among the responders who used ECs at baseline. In Grana 2014b the one-year abstinence rate was 10% (9/88) in smokers who had used ECs (at least once in the last 30 days) at baseline, compared with 13.8% (119/861) in non-EC users. The difference between EC and non-EC users was not statistically significant. No information was provided on whether people were using ECs for the purpose of cessation or reduction prior to baseline, or whether they used any EC at all during the follow-up period. Choi 2014 only reported that 11% of smokers who had used ECs for one day or more in the last 30 days at baseline had quit smoking at one-year follow-up, compared with 17% of smokers who had never used ECs. After adjusting for demographics and baseline cigarette consumption, the odds of quitting were not significantly different between EC users and people who had never used ECs (OR 0.93, 95% CI 0.19 to 4.63). Again, no information was provided on whether the participants used ECs during the follow-up period. The Etter, Grana and Choi studies share a serious limitation. As these studies only recruited current smokers, they excluded those people from the same population who tried ECs and stopped smoking (e.g. if 100 smokers tried ECs and 50 stopped smoking, these studies would only recruit the 50 who continued to smoke). Following up 'treatment failures' is likely to show a low treatment effect, even for treatments that are highly effective. To asses the effects of ECs on smoking, participants need to be recruited prior to initiating EC use.

Reduction

We dichotomised data from studies showing the proportion of participants who did not manage to stop smoking, but achieved a 50% or greater reduction in baseline cigarette consumption versus those who did not. Participants who were abstinent were not included in the 50% or greater reduction group, and are removed from the denominator for each arm when calculating the RR.

Randomized controlled trials

In the ASCEND trial (Bullen 2013) the difference in the proportion of people that achieved a 50% or more reduction between nicotine and placebo EC users was borderline statistically significant (RR 1.31, 95% CI 1.00 to 1.70, Analysis 2.1). A significantly higher proportion of EC users, compared with patch users, achieved a 50% or more cigarette reduction (57% vs 41%; RR

1.41, 95% CI 1.20 to 1.67, Analysis 2.2). Overall, nicotine EC users reduced consumption by an average of 9.7 (standard error (SE) 0.4) cigarettes per day, compared to a reduction of 7.7 (SE 0.4) in patch users (P = 0.002). In this study only self-reported abstainers were asked to undertake a CO breath test, so these self-reported changes in cigarette consumption are not objectively validated.

The ECLAT trial (Caponnetto 2013a) found that 25.5% of nicotine EC users versus 16% of placebo EC users achieved 50% or greater reduction in smoking at one year (RR 1.30, 95% CI 0.70 to 2.44, Analysis 2.1).

We combined the self-reported reduction data from the two studies and found that nicotine EC use was associated with a significantly higher likelihood of reducing cigarette consumption by at least half when compared with placebo EC groups (RR 1.31, 95% CI 1.02 to 1.68, Analysis 2.1; 612 participants).

Cohort studies

Data regarding smoking reduction are summarised in Table 2.

In smokers that were unmotivated to quit, a third (32.5%) achieved sustained reduction of 50% or more for at least 30 days at six months, reducing to 27.5% at both 18 and 24 months (Polosa 2011). At six months, the reducers cut their median cigarette consumption from 25 [interquartile range (IQR) 20 - 30] to 6 [IQR 5 - 6], and their CO from 18 [IQR 14 -3 3] ppm to 8 [IQR 6 - 11] ppm. Both changes were statistically significant (P < 0.001 and P = 0.001 respectively). Among the reducers at 24 month follow-up similar changes were also observed (cigarette consumption: 24 [IQR 19 - 27.5] to 4 IQR [4 - 5], P = 0.003; CO 24 [IQR 17 - 36.5] to 10 [IQR 8.5 - 12], P = 0.006).

Half (7/14) of the cohort of smokers with schizophrenia achieved a sustained reduction of 50% or more for at least 30 days at 12 months (Caponnetto 2013b). Within this group, median daily cigarette consumption reduced from 30 [IQR 30 - 60] to 15 [IQR 10 - 20] (P = 0.018), and CO from 32 [IQR 22 - 39] to 17 [IQR 11 - 20] ppm (P = 0.028).

In the cohort of smokers with asthma, mean cigarette consumption decreased over a period of 12 months from 21.9 to 1.7 (P < 0.001) in all users, and from 22.4 to 3.9 (P < 0.001) in the dual users (Polosa 2014).

In a cohort of people recruited from primary care who were trying to quit (Ely 2013), 27.1% of participants achieved a reduction of 50% or more at six months.

Etter 2014 reported no significant change in cigarette consumption between baseline and one-year follow-up in people who used ECs and smoked both at baseline and at follow-up. Grana 2014b found no association between the history of EC use at baseline and change in cigarette consumption in people who smoked at both time points. Choi 2014 reports no difference in change in cigarette consumption between baseline and one-year follow-up between smokers who had used ECs at baseline and those who had not. However, relevant data on EC use during the follow-up period are not reported.

Adverse events

None of the RCTs or cohort studies reported any serious adverse events (SAEs) that were considered to be plausibly related to EC use.

Of the people available for 6-month follow-up in the ASCEND trial (Bullen 2013) 44.4% of participants in the nicotine EC arm reported any AEs, compared with 44.7% and 45.6% in the patch and placebo EC arms respectively. Differences were not statistically significant (nicotine vs placebo EC: RR 0.97, 95% CI 0.71 to 1.34, Analysis 3.1; nicotine EC vs patch; RR 0.99, 95% CI 0.81 to 1.122, Analysis 3.2).

The ECLAT trial (Caponnetto 2013a) found no difference in frequency of AEs at 3- or 12-month follow-up between the three groups. AEs were also measured at baseline, with the five most frequently reported being cough (26%), dry mouth (22%), shortness of breath (20%), throat irritation (17%), and headache (17%). In all groups the frequency of AEs decreased significantly over time, with the exception of throat irritation.

The cohort studies show a similar picture, with mouth and throat irritation being the most frequently reported AEs in EC users, dissipating over time. In Nides 2014, where participants used ECs for one week, 12 participants experienced 15 AEs and all but one (throat irritation) were classified as mild. After two weeks of use, Van Staden 2013 documented that 54% of participants (7/13) reported reduction in phlegm compared with baseline, whilst 31% (4/13) reported an increase. Changes in phlegm product could also be secondary to stopping smoking (the majority also reported an improved sense of taste, smell and an increase in appetite). There was one drop-out due to illness (headache and fever), but it is unclear if this was deemed to be related to EC use or not. Humair 2014 reports only that participants did not experience any AEs.

Three studies (McRobbie 2014; Polosa 2014; Van Staden 2013) report the effects of at least one week of EC use on more specific parameters.

McRobbie 2014 assessed the change in 3-HPMA, the main metabolite of acrolein, excreted in urine after four weeks of EC use. Acrolein is a carcinogen and is present in cigarette smoke and some EC vapour (Bein 2011). There is a concern that people that use EC *and* smoke may be exposed to higher levels of acrolein than smoking alone. Of the 33 people that completed four-week follow-up, 16 were EC users only, and 17 were dual users. Both groups showed a significant decrease in 3-HMPA in ng/mg creatinine (EC users: 1623 [standard deviation (SD) 850] to 343 [SD 178], P < 0.001; Dual users: 2443 [SD 1105] to 969 [SD 807], P < 0.001). Carbon monoxide levels (ppm) also showed a significant decrease over time in both groups (EC users: 15 [SD 8] to 3 [SD 2], P < 0.001; Dual users: 23 [SD 11] to 11 [SD 8], P = 0.001). Urinary cotinine (ng/mg creatinine) also decreased in both groups

(EC users: 1073 [SD 832] to 889 [SD 959], P = 0.486; Dual users: 2203 [SD 1734] to 1227 [SD 679], P = 0.001).

In the retrospective study of smokers with asthma who had become regular EC users (Polosa 2014), there was no evidence of harm. On the contrary, there were significant improvements in asthma control, measures of lung function, and airways hyperresponsiveness both in EC users only (n = 10) and in dual users (n = 8) over the 12-month follow-up period. There was a slight decrease in the number of asthma exacerbations, but this was not statistically significant (1.17 to 0.78, P = 0.153).

The outcomes of Van Staden 2013 showed that smokers who switched to ECs had significant improvement in blood oxygen saturation (96.15% [SD 1.76] to 97.49% [SD 1.34]; 1.34% increase, 95% CI 0.60 to 2.08; P = 0.002) and reduction in arterial (1.95%; 95% CI 0.47 to 3.44; P = 0.01) and venous (1.87%; 95% CI 0.38 to 3.36; P = 0.02) carboxyhaemoglobin levels.

DISCUSSION

Summary of main results

A meta-analysis that pooled the results of two randomized controlled trials (RCTs), covering 662 participants, showed that smokers who used nicotine electronic cigarettes (ECs) were significantly more likely to stop smoking than smokers using placebo ECs. The effect size (5%) is small, but not unusual given the low level of behavioural support provided. There was no evidence of statistical heterogeneity, despite the differences in study designs. In the one trial that evaluated it, a first-generation EC with low nicotine delivery was as effective as nicotine patches at helping smokers to quit long-term, but confidence intervals were wide.

In terms of reduction in cigarette consumption, nicotine-containing ECs were significantly more effective than placebo ECs and also significantly more effective than nicotine patches in helping people achieve 50% or greater reduction in smoking. The finding is tempered by lack of biochemical confirmation of the reduction. Future studies should include such measures. There was evidence from intervention cohort studies that dual use may promote smoking reduction, and no evidence that dual use undermined smoking cessation.

Although the two randomized controlled trials were well conducted and judged to be at low risk of bias, the quality of the evidence overall is categorised as low, because of the small number of trials on which it is based (see Summary of findings for the main comparison). We would be more confident in the findings were there more studies available.

None of the included studies reported serious adverse events that were related to EC use, nor did any studies detect a significant increase in adverse events in people using ECs. The most commonly reported AEs were local irritation of the throat and mouth. One of the RCTs (Caponnetto 2013a) measured AEs at baseline and then across the study duration, and showed that the frequency of respiratory symptoms (e.g. cough and shortness of breath) decreased over time, which is likely to be secondary to changes in cigarette smoking.

Overall completeness and applicability of evidence

This is a new and rapidly evolving field of research. Our search methods captured almost 600 publications. While we are confident that this represents the full range of data for the time period searched, there may be unpublished studies that we did not find. Despite the large number of publications returned, there were relatively few that contain empirical data and met our inclusion criteria.

We relied predominantly on RCTs for smoking cessation and reduction outcomes. Only two have been published to date. This limits the strength of our conclusions. We were unable to do many of the planned analyses because of insufficient data.

The designs of the two published RCTs limit the interpretation of the findings. The ECLAT study (Caponnetto 2013a) used only a placebo EC control, which does not allow comparison with standard smoking cessation treatments. The ASCEND trial (Bullen 2013) was more pragmatic, but also has some limitations. For example, few people accepted the offer of telephone-based behavioural support. This is a likely reason for low absolute abstinence rates across all arms. The pragmatic nature of the study also resulted in some differences in the way that participants received their allocated product (EC was couriered directly to participants, whereas nicotine patches were supplied via a voucher that participants had to take to a community pharmacist). This approach has been criticised, as this difference may have influenced the outcomes (Grana 2014a). However the trial was trying to replicate standard practice, and sensitivity analyses did not suggest that this was a confounding factor.

Both studies used first-generation cartridge 'cigalike' ECs that were widely available at the time but that have been surpassed by newer models. The EC used in the ASCEND trial (Bullen 2013) delivered little nicotine and not particularly quickly (C_{max} of 1.3 ng/ml was achieved after 10 minutes of use). The EC used in the ECLAT trial (Caponnetto 2013a) also performed poorly and was discontinued before the trial was published. This may have yielded a more conservative estimate than would be seen with newer models. If these poorly performing EC products can assist smokers, products with better nicotine delivery may have better effects.

Much of the cohort data we used in this review is from one team and it would therefore be useful to see these results replicated by others. It is reassuring, however, to see that different populations studied (e.g. smokers with and without mental illness) have a similar response in terms of EC use on smoking behaviour.

The adverse effects described in both the RCT and cohort studies are similar, regardless of the brand of EC used. They also reflect what is reported in survey data (Dawkins 2013b; Etter 2011), so we believe that they are broadly applicable to most EC brands. The common adverse effects, i.e., mouth and throat irritation, are likely to be caused by the propylene glycol (a humectant) and nicotine, which has a distinctive hot/peppery taste.

There has been concern raised that dual use may expose people to greater health risks, including higher nicotine levels. However, given that people who smoke like to maintain relatively stable blood nicotine levels (Russell 1990), receiving nicotine from an alternative source (i.e., EC) is likely to reduce nicotine intake from cigarettes, which should be accompanied by a reduction in smoke and toxin intake. In the single study that assessed biochemical changes in dual users, there was a significant decrease in cotinine, exhaled carbon monoxide levels, and urinary 3-HMPA (McRobbie 2014).

Quality of the evidence

The RCTs from which we extracted data for this review were conducted to a high standard, with adequate randomization, treatment allocation and blinding, and the abstinence data are reported in line with accepted standards, including biochemical validation of self-reported smoking status. We consider these studies to be at an overall low risk of bias. However, as there were only two of them, the body of evidence is limited and is considered to be low or very low quality by GRADE standards, because of the small number of trials. These GRADE ratings reflect low levels of confidence in the effect estimates presented in this review. This low level of certainty in the findings does not reflect issues with the quality of the individual studies, but rather reflects imprecision arising from low event rates and wide confidence intervals around the estimated effects, and some indirectness due to poor nicotine delivery in one of the devices tested.

It was unclear if the ECLAT trial (Caponnetto 2013a) intended to combine the two EC arms in the analysis or not. In sample size calculation they compared ECs with placebo ECs, but results are not reported in this way. The rationale for examining two very similar EC arms is not obvious to the review authors.

Both RCTs were underpowered. The sample for the ASCEND trial (Bullen 2013) was based on absolute six month quit rates of 20% and 30% for the patch and nicotine EC groups respectively. The effect size was estimated from the meta-analysis of NRT trials, but the estimated patch group 20% quit rate, which was estimated from previous research undertaken in New Zealand where participants were recruited from among callers to the national Quitline, was clearly too optimistic. The ASCEND study recruited directly from the community and this population may not have been as committed to quitting, or the national Quitline data were based on a less rigorous standard (e.g., unvalidated self-reported abstinence rate). The ECLAT trial (Caponnetto 2013a) also overestimated expected abstinence rates and the subsequent sample size (n = 300) was insufficient to detect significant differences.

The cohort studies that we included were all deemed to have high risks of bias, which is inherent in the study design. Some studies did not define abstinence outcomes or validated self-reported smoking status, which further lowers our confidence in the findings. In addition, two studies (Choi 2014; Grana 2014b) did not report on the nicotine content of the EC used. Data presented from these studies therefore needs to be interpreted with caution.

We excluded a number of studies at the full-paper screening stage because they did not contain any useable data, had significant limitations, or had only short-term EC use.

A major limitation common to several cohort studies (e.g. Choi 2014; Dutra 2014; Lee 2014; Popova 2013) is the definition of EC use, which is generally categorised as 'ever use' (e.g. ever tried, even just once) and 'current' use (used on at least one day in the last 30 days). 'Ever use' identifies experimentation, but oddly experimentation within the last 30 days would be captured as current use. Studies were also unclear on the reasons for EC use (e.g., as part of a quit attempt, trying the new product out of curiosity, or to use when they cannot smoke) and failed to take into account other relevant factors (e.g., level of dependence) in their analyses. Perhaps most importantly, these studies excluded EC users who stopped smoking and so only followed up 'treatment failures'. Inherent to all cross-sectional studies is the difficulty of establishing a temporal association. Causation cannot be inferred.

Potential biases in the review process

We consider the review process used to be robust and do not believe we have introduced any biases. Our search strategy included the Cochrane Tobacco Addiction Group Specialised Register and we were able to capture a number of ongoing studies. However, there may be unpublished data that our searches did not uncover. We also considered participants lost to follow-up as smokers, which is best practice in this field of work.

Agreements and disagreements with other studies or reviews

This is the first review of ECs that has pooled data and conducted a meta-analysis. The findings are in line with a recent comprehensive review of the EC literature (Hajek 2014). Our findings are also in agreement with those of a large, representative, population survey (Brown 2014a). Although cross-sectional in design, it examined self-reported abstinence rates among people that had smoked within the previous 12 months and made at least one quit attempt during that period with either an EC, NRT purchased over-the-counter or nothing in their most recent quit attempt. After adjusting for key potential confounders, including nicotine dependence, smokers attempting to stop smoking with the help of

ECs were more likely to succeed than those using NRT or trying to quit unaided.

Our findings, however, are in disagreement with another review that was commissioned by the World Health Organization, and later published (Grana 2014a). To examine the association between EC use and smoking cessation, the authors pooled data from five population-based studies (four longitudinal and one cross-sectional), and reported that EC use was associated with a significantly lower chance of quitting smoking (OR 0.61, 95% CI 0.50 to 0.75). We excluded three (Adkison 2013; Popova 2013; Vickerman 2013) of these studies from our review. Popova 2013 was excluded because of a cross-sectional design. Whilst Adkison 2013 use a longitudinal design, participants were only asked about EC use at follow-up, and so for the purpose of our outcomes of interest, we considered this as a cross-sectional study. Vickerman 2013 was not a longitudinal study, but surveyed people at seven months after enrolment into a Quitline service and asked them about EC use retrospectively. Of those that reported ever using ECs (30.9%), the majority (72%) had only used them in the past six months. 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, like the surveys by Grana and Choi, this only included 'treatment failures' and cannot determine the effects of EC use overall. Grana 2014b and Choi 2014, which did use a longitudinal design and which are included both in our review and in Grana 2014a, did not detect a significant difference in smoking cessation between smokers that used or did not use ECs at baseline but, as noted above, only those smokers who did not stop smoking after using ECs were followed up. These studies are also limited by their definition of EC use at baseline. As per the original protocol for this review, we focused on evidence from randomized controlled trials for cessation and reduction outcomes, although we also analysed cohort studies which provided interpretable data.

AUTHORS' CONCLUSIONS

Implications for practice

A limited number of randomized trials have been reported, so certainty about the effects is low. More data are needed to strengthen confidence in the estimates. There is evidence from the pooled results of two trials that electronic cigarettes (ECs) with nicotine, compared with placebo ECs, helped smokers to stop smoking long-term; they also increased the number of people who did not quit altogether to halve cigarette consumption. This corresponds to findings from placebo-controlled trials of NRT (Stead 2012).

There is evidence from one trial that ECs may lead to similar quit rates at six months as NRT, but the confidence interval is wide. ECs are an evolving technology and newer devices may be more effective, but research is needed to confirm this.

There is evidence from this same trial that nicotine ECs may lead to a greater proportion of participants reducing cigarette consumption by at least 50% at six months than the use of NRT.

The included studies did not identify any serious adverse effects associated with short- to medium-term (up to two years) use of ECs. The most commonly reported adverse effects were irritation of the mouth and throat.

Implications for research

Although the gold standard in examining the efficacy of medicines, including those used to help people stop smoking, is to compare active treatment with placebo, testing ECs containing nicotine against ECs without nicotine presents a rather conservative paradigm. This is because ECs provide nicotine replacement as well as behavioural and sensory replacement for cigarettes. As both of these elements are likely to be active ingredients of EC effects, 'placebo-controlled' trials are in effect subtracting the sensorimotor element from EC efficacy. Although these sensorimotor effects may be important to many smokers, we do not know how much they might enhance quit rates. Existing evidence suggests that this may be only small (Bullen 2013; Przulj 2013). Although placebo ECs were important in testing ECs with metrics used in evaluating NRT products, future studies should focus on comparing ECs with 'usual care' or minimal treatment, and with alternative pharmacological and behavioural 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.

Given the variety of EC products on the market and the product evolution, future studies need to select ECs with good nicotine delivery that are representative of the best current standard in terms of reliability and user satisfaction.

Further RCTs also need to be adequately powered, and to consider providing ECs in a way that would be used in real-world settings (e.g., taking into account individual preferences for strengths and flavours of e-liquids and even EC devices).

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Bullen 2013

Methods	**Design:** 3 parallel groups RCT **Recruitment:** Smokers recruited from the community, via newspaper advertisements **Setting:** Research Unit, New Zealand **Inclusion Criteria:** 18 years of age or older; Smoked 10 or more cpd over past year; Wanted to stop smoking **Exclusion Criteria:** pregnant and breastfeeding women, people using cessation medicines or using other support to quit, heart attack, stroke, severe angina in the last 2 weeks, poorly-controlled medical disorder, allergies, other chemical dependence
Participants	Total N: 657 62% women, mean age 42, % NZ Maori, smoking 18 cpd, mean FTND score 5.5 Lost to follow-up at 6 months: • NEC: 43/289 • PATCH: 58/295 • PEC: 15/73 Discontinued treatment: • NEC: 4/289 • PATCH: 22/295 • PEC: 1/73
Interventions	randomized 4:4:1 to NEC, PATCH or PEC use for 13 weeks (from 1 week prior to TQD) • NEC: Elusion brand 16 mg cartridges; sent product via courier • PATCH: 21 mg/24-hour patch; sent voucher to exchange for NRT at pharmacy (dispensing costs covered) • PEC: As per EC but 0 mg cartridges All participants referred to Quitline and received an invitation to access phone- or text-based support. This was accessed by < 10%
Outcomes	Sustained (≤ 5 cigarettes allowed) validated (exhaled breath CO < 10 ppm) abstinence at 6 months ≥ 50% self-reported reduction in baseline cigarettes at 6 months Participants reporting any adverse events Propotion of AEs that were serious Proportion of unrelated AEs
Notes	Accessed support: NEC: 115/289; PATCH: 106/295; PEC: 26/73

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerised block randomization

Bullen 2013 (*Continued*)

Allocation concealment (selection bias)	Low risk	Computerised via study statistician
Blinding of participants and personnel (performance bias) All outcomes	Low risk	NEC and PEC were blind to treatment condition in relation to one another. No blinding for NEC/PEC vs PATCH conditions, but as NEC and PATCH were both active treatments performance bias judged unlikely
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation used
Incomplete outcome data (attrition bias) All outcomes	Low risk	LTFU 22% (all considered smokers). Patch group had a higher LTFU and withdrawal than EC (loss to follow-up 17% NEC, 27% patches, 22% PEC). However, minimal difference in per-protocol and ITT analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	None noted

Caponnetto 2013a

Methods	**Design:** 3-arm double-blind randomized controlled trial: EC with 7.2 mg nicotine for 12 weeks; same for 6 weeks followed by 5.2 mg for 6 weeks: EC with no nicotine for 12 weeks **Recruitment:** Newspaper advertisements **Setting:** Outpatient clinic, Italy **Inclusion Criteria:** Smoked at least 10 cpd for past 5 years; age 18 - 70; in good health; not currently or intending to quit smoking in the next 30 days **Exclusion Criteria:** symptomatic cardiovascular or respiratory disease; regular psychotropic medicine use; current or past history of alcohol abuse; use of smokeless tobacco or NRT; pregnant or breast feeding
Participants	Total N: 300 36% women, mean age 44 (SD 12.5), mean cpd 20 (IQR: 15 - 25) Lost to follow-up at 12 months • Grp A: N = 35/100 • Grp B: N = 37/100 • Grp C: N = 45/100 No participants discontinued intervention
Interventions	EC presented as a healthier alternative to tobacco smoke and could be freely used, ad libitum (up to 4 cartridges per day) for 12 weeks, as a tobacco substitute EC used: 'Categoria' (model 401) with disposable cartridges

	• Grp A: 12 weeks of 7.2 mg capsules ('Original') • Grp B: 6 weeks 7.2 mg ('Original') then 6 weeks 5.4 mg ('Categoria') • Grp C: 12 weeks of 0 mg ('Original') Baseline visit and up to 7 follow-up visits to receive more cartridges, hand in diaries, measure CO and vital signs
Outcomes	Abstinence at 12 months (complete self-reported abstinence from tobacco smoking since previous visit at 6 months, confirmed with CO < 7 ppm at 12 months) ≥ 50% reduction in baseline cigarettes at 12 months Recorded AEs thought to be related to tobacco smoking and EC at baseline and at each study visit (7 follow-up visits over 12 weeks, plus at 24 and 52 weeks)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated, block size 15 (5:5:5 ratio)
Allocation concealment (selection bias)	Low risk	randomization carried out by pharmacy, who did not have direct contact with the participants
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Double-blind. "Blinding was ensured by the identical external appearance of the cartridges. The hospital pharmacy was in charge of randomization and packaging of the cigarettes"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation used
Incomplete outcome data (attrition bias) All outcomes	Low risk	211 (70.3%) and 183 (61%) attended 6- and 12-month follow-up (at 12m, 35% lost in 7.2 group; 37% lost in 5.4 group; 45% lost in no-nicotine group)
Selective reporting (reporting bias)	Unclear risk	Unclear if original intention was to combine groups A+B or not. In sample size calculation they compared A+B with C, but results are not reported in this way
Other bias	Unclear risk	None noted

Caponnetto 2013b

Methods	**Design:** Prospective cohort **Recruitment:** Inpatients at a psychiatric institution in Italy **Inclusion criteria:** Smoked ≥ 20 cpd for at least the past 10 years; diagnosis of schizophrenia **Exclusion Criteria:** Alcohol and illicit drug use, recent myocardial infarction, angina pectoris, high blood pressure (BP > 140 mmHg systolic or 90 mmHg diastolic, or both) , diabetes mellitus, severe allergies, poorly-controlled asthma or other airway diseases
Participants	Total N: 14 57% women, mean age 44.6 (SD 12.5), mean pack years smoked 28.8 (SD 12.9)
Interventions	Seen at baseline, given EC ('Categoria' brand) with an initial 4-weeks supply of 7.4 mg nicotine cartridges. Instructed to use ad libitum up to 4 cartridges per day. EC cartridges supplied at months 1, 2, and 3 No instruction on cessation or reduction was provided.
Outcomes	Follow-up at 1, 2, 3, 6 and 12 months where cigarette consumption, CO, AEs and positive and negative symptoms of schizophrenia were measured Sustained reduction of ≥ 50% for at least 30 days at 12 months 30-day point prevalence CO-validated abstinence at 12 months Adverse events
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort; no randomization
Allocation concealment (selection bias)	High risk	Not randomized
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation used
Incomplete outcome data (attrition bias) All outcomes	Low risk	0/14 lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes
Other bias	Unclear risk	None noted

Choi 2014

Methods	**Design:** Longitudinal survey (data from the Minnesota Adolescent Community Cohort) **Recruitment:** Participants selected via cluster random sampling of household phone numbers **Setting:** Telephone survey **Inclusion criteria:** Participants who completed the survey between October 2010 and March 2011 and provided follow-up data one year later **Exclusion Criteria:** none stated
Participants	Total N: 346
Interventions	Observational; no specific intervention. No data on nicotine content of ECs are provided
Outcomes	Self-reported smoking cessation at 1-year follow-up (not otherwise defined)
Notes	This publication is a letter in response to a comment on the authors' original paper Choi 2014, and the details on methods are taken from this.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Although there is no blinding, the study design and lack of intervention or contact with researchers mean that there is unlikely to be significantly impact on performance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although there is no blinding, the study design and lack of intervention or contact with researchers mean that there is unlikely to be significantly impact on detection
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Unable to determine attrition bias
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes
Other bias	Unclear risk	None noted

Ely 2013

Methods	Design: Prospective cohort Recruitment: Letter sent to family practice patients who were current smokers Setting: Single family practice, Colorado USA Inclusion criteria: want to quit or switch from tobacco cigarettes to ECs Exclusion Criteria: none reported
Participants	Letters sent to 640 patients, 48 chose to participate and 44 completed the programme, 4 were lost to follow-up Of the 44 participants, 66% women, all non-Hispanic/white, aged 20 - 75 (30% were age 51 - 60), 57% had a high school education or less
Interventions	The 6-month smoking cessation programme was based on The '5 A's' model and trans-theoretical model. Options for treatment were discussed with each participant at the start of the programme. All used an EC with 16 using bupropion and 2 using varenicline as well Participants were provided with written information on "blu cig" and "smoke tip" ECs, regarding cost, availability, nicotine dosage options
Outcomes	Phone follow-ups at 2 weeks, 1 month, 3 months, and 6 months At completion of programme (using ITT) Abstinence from smoking and EC use Abstinence from smoking but not EC use $\geq$ 50% reduction of baseline cigarette consumption (still using ECs)
Notes	No definition of abstinence provided Not clear if 'completed programme' was at 6 months.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	4/48 lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes

Ely 2013 (*Continued*)

Other bias	High risk	No definition of abstinence provided Not clear if 'completed programme' was at 6 months.

Etter 2014

Methods	**Design:** Longitudinal Internet survey **Recruitment:** Via websites selling or informing about ECs and online EC forums **Setting:** Online survey (open to all nationalities; of respondents, 34% US, 24% France, 8% UK, 6% Switzerland, 28% other countries) **Inclusion criteria:** Aged 18 years and older **Exclusion Criteria:** none stated
Participants	**One month survey** Total N: 477, mean age 42, 41% women, 59% had a diploma giving access to university, 28% daily or occasional smokers, 76% daily EC users. 50/477 occasional or daily smokers at baseline **One year survey** Total N: 367, mean age 43, 42% women, 59% had a diploma giving access to university, 24% daily or occasional smokers, 79% daily EC users. 35/367 occasional or daily smokers at baseline
Interventions	Observational; no specific intervention. Participants that had completed a baseline questionnaire were emailed one month and one year later and asked to provide follow-up data on EC use and smoking behaviour
Outcomes	From among those that were smoking cigarettes at baseline 7-day point prevalence abstinence from smoking at 12 months Smoking consumption (change from baseline) at 12 months
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Although there is no blinding, the study design and lack of intervention or contact with researchers mean that there is unlikely to be significantly impact on performance

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although there is no blinding, the study design and lack of intervention or contact with researchers mean that there is unlikely to be significantly impact on detection
Incomplete outcome data (attrition bias) All outcomes	High risk	28% (N = 367) for those who answered the baseline survey (N = 1329) provided data at 1-year follow-up
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes
Other bias	Unclear risk	None noted

Grana 2014b

Methods	**Design:** Longitudinal web-based survey **Recruitment:** Via Knowledge Networks (now GfK) probability-based web-enabled panel **Setting:** Web-based survey, USA **Inclusion criteria:** Aged 18 years and older **Exclusion Criteria:** none stated
Participants	Total N: 949 52.4% women 90.8% having at least a high school education, 75.3% white, mean (SD) daily cigarette consumption 14.5 (9.7), 59% smoke within 30 minutes of waking, 69. 4% never expecting to quit or intending to quit in the next 6 months 90.7% did not use (EC use within the last 30 days) an EC at baseline. No data on nicotine content of EC are provided
Interventions	Observational; no specific intervention
Outcomes	Self-reported smoking cessation at 1-year follow-up (not otherwise defined)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Although there is no blinding, the study design and lack of intervention or contact with researchers mean that there is unlikely to be significantly impact on performance

Grana 2014b (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Although there is no blinding, the study design and lack of intervention or contact with researchers mean that there is unlikely to be significantly impact on detection
Incomplete outcome data (attrition bias) All outcomes	Low risk	81.3% of the participants of baseline survey completed follow-up survey
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes
Other bias	Unclear risk	None noted

Humair 2014

Methods	**Design:** Prospective cohort **Recruitment:** People attending an outpatient clinic **Setting:** University hospital outpatient clinic, Switzerland **Inclusion criteria:** Wish to reduce tobacco use or had failed to stop smoking using varenicline, bupropion or NRT in past
Participants	TOTAL N: 17 mean 23 cpd, 82% had a psychiatric illness
Interventions	Offered an EC with nicotine 59% also reported using NRT or varenicline in addition to EC
Outcomes	Smoking cessation and reduction by at least 30% at 12 months (self report) Adverse events No significant side effects
Notes	Abstract only, hence little detail available Not clear if EC was provided by clinic or if participants had to buy their own

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding

Blinding of outcome assessment (detection bias) All outcomes	High risk	No blinding, no biochemical validation used
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Numbers lost to follow-up not reported
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes
Other bias	Unclear risk	None noted

McRobbie 2014

Methods	**Design:** Prospective cohort **Recruitment:** advertisements in free London newspapers **Setting:** Smokers' clinic, East London, UK **Inclusion criteria:** Daily smokers who want to quit, aged 18 and older **Exclusion Criteria:** pregnant and breastfeeding women, current serious medical illness, EC use for more than 1 week in the past
Participants	Total N: 40 45% women, mean age 47 (SD 12), mean cpd 19 (SD 10), mean FTND 5.2 (SD 2.8), 65% in full-time employment
Interventions	Participants attended baseline session 1 week prior to their TQD. On the TQD, participants were provided with an EC (Green Smoke, 1st generation device, 2.4% nicotine cartridges). 2 cartridges per day were supplied initially, with the supply adjusted to actual use later. Attended 4 weekly follow-up sessions and received standard behavioural support
Outcomes	Cigarette consumption and CO readings collected at each session. Urine sample for cotinine and 3-HPMA analysis collected at baseline and 4 weeks post-TQD Change in urinary 3-HPMA (ng/mg creatinine) at 4 weeks Change in urinary cotinine (ng/mg creatinine) at 4 weeks Change in CO at 4 weeks
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized

McRobbie 2014 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation used
Incomplete outcome data (attrition bias) All outcomes	Low risk	7/40 participants were lost to follow-up
Selective reporting (reporting bias)	Low risk	All predefined outcomes reported.
Other bias	Unclear risk	None noted

Nides 2014

Methods	**Design**: Open-label non-comparative study **Setting**: Clinical Trials Unit, USA **Recruitment**: Study site database and community advertisements **Inclusion criteria**: age 18 - 65 years; good health; BMI 18 - 35; smoking 10+ cpd; and CO > 10 ppm **Exclusion criteria**: pregnancy or breastfeeding; other drug dependency; use of any psychiatric or opioid medications; EC within the previous 14 days; use of NRT in last 30 days; want to reduce or quit smoking within the next 30 days
Participants	Total N: 29 44% women; mean age 43; mean cpd 20.1; mean FTND 4.5
Interventions	Participants attended 3 clinic visits at 1-week intervals Visit 1: Baseline Visit 2: Provided with 1st generation type - 'NJOY® King Bold' (NJOY, Inc., Scottsdale, AZ), with 26 mg nicotine. Used ad libitum for 20 minutes in the clinic, then ad libitum use over the next week. Recorded use of regular cigarettes and puffs on EC Visit 3: Participants abstained from all sources of nicotine for 12 hours prior to visit
Outcomes	Adverse events.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized

Nides 2014 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation used
Incomplete outcome data (attrition bias) All outcomes	Low risk	2 participants dropped out between visits 1 and 2.
Selective reporting (reporting bias)	Low risk	Planned comparisons reported
Other bias	Unclear risk	None noted

Polosa 2011

Methods	**Design:** Prospective cohort **Recruitment:** Advertisments in local hospital in Catania, Italy **Inclusion criteria:** Healthy smokers 18 - 60 years old, smoking ≥ 15 cpd for at least the past 10 years, and not wanting to quit smoking at any time in the next 30 days **Exclusion Criteria:** History of alcohol and illicit drug use, psychiatric illness, recent myocardial infarction, angina pectoris, high blood pressure (BP > 140 mmHg systolic or 90 mmHg diastolic, or both), diabetes mellitus, severe allergies, poorly-controlled asthma or other airways diseases
Participants	Total N: 40, hospital staff 35% women, mean age 42.9 (SD 8.8), median cpd 25 (IQR 20 - 30), median FTND 6.0 (IQR 6 - 8)
Interventions	Seen at baseline, given EC ('Categoria' brand) with an initial 4-week supply of 7.4 mg nicotine cartridges. Instructed to use ad libitum up to 4 cartridges per day. EC cartridges supplied at months 1, 2, and 3 No instruction on cessation or reduction was provided
Outcomes	Follow-up at 1, 2, 3, and 6 months where cigarette consumption, CO, and AEs were measured Sustained reduction of ≥ 50% for at least 30 days at 6 months Sustained reduction of ≥ 80% for at least 30 days at 6 months 30-day point prevalence CO-validated abstinence at 6 months Follow-up at 18 and 24 months where cigarette consumption, CO, and AEs were measured Sustained reduction of ≥ 50% from baseline at 18 & 24 months Sustained reduction of ≥ 80% from baseline at 18 & 24 months CO-validated abstinence at 18 & 24 months (not otherwise defined) Adverse events

Polosa 2011 (*Continued*)

Notes	13 people were lost to follow-up Smoking cessation services provided to those who spontaneously asked for assistance with quitting. These subjects were excluded from the study protocol

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemical validation
Incomplete outcome data (attrition bias) All outcomes	Low risk	13/40 were lost to follow-up, but used ITT analysis
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes
Other bias	Unclear risk	None noted

Polosa 2014

Methods	**Design:** Retrospective cohort (retrospective audit of clinical records) **Recruitment:** Review of medical records from a respiratory outpatient clinic in Italy from September 2012 until December 2013 **Setting:** Respiratory outpatient clinic, Italy **Inclusion criteria:** People with mild to moderate asthma reporting regular EC use on at least 2 consecutive follow-up visits **Exclusion criteria: N**one reported
Participants	Total N: 18, 39% (N = 7) women 10 were using EC only (3 women, mean age 36) 8 used ECs and smoked $\leq$ 5 cpd (4 women, mean age 42) Both groups smoked 22 cpd at baseline Duration of EC use 10 - 14 months. N = 12 using them for > 1 year All started on 1st generation EC, but the 'majority' switched to a 'personal vaporiser' (2nd or 3rd generation)
Interventions	Observational; no specific intervention. First 2 observations prior to EC use, second 2 observations during EC use

Outcomes	Data from 4 clinic visits were collected: (1) pre-baseline (6 - 12 months prior to baseline) ; (2) baseline; (3) 6 (± 1) month follow-up; and (4) 12 (± 2) month follow-up. Visits 1 and 2 were pre-EC use and visits 3 and 4 were during EC use At each visit, participants were assessed by clinical history and examination and re-evaluation of treatment adherence and efficacy 1. Juniper's Asthma Control Questionnaire (ACQ) score 2. Number of exacerbations from the previous follow-up visit (defined as an increase in respiratory symptoms requiring a short course of oral or parenteral corticosteroids) 3. Forced expiratory flow in 1 second (FEV1) 4. Forced vital capacity (FVC) 5. Expiratory ratio (% FEV1/FVC) 6. Forced expiratory flow at the middle half of the FVC (FEF 25 - 75%); 7. Bronchial provocation tests assessing Airway HyperResponsiveness (AHR) with methacholine (some participants only)
Notes	Changes in lung function tests: FEV1 (L): 3.30 (± 0.78) to 3.40 (± 0.73), P = 0.005 FVC (L): 4.28 (± 0.90) to 4.43 (± 0.78), P = 0.006 FEF 25 - 75% (L/sec.): 2.75 (± 0.72) to 3.11 (± 0.57), P = 0.001 ACQ: 2.03 (± 0.37) to 1.47 (± 0.20), P < 0.001 PC20 (mg/mL): 1.24 (0.49, 3.27) to 2.56 (0.5, 5.55), P = 0.003

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Retrospective cohort
Allocation concealment (selection bias)	High risk	Self-selected sample
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	No biochemical validation undertaken
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not applicable; unclear if some participants attended first 3 visits but not 4th, and hence were excluded
Selective reporting (reporting bias)	High risk	Unable to determine prespecified outcomes
Other bias	Unclear risk	None noted

Van Staden 2013

Methods	**Design:** Single-group within-subject design **Recruitment:** Participants from a military hospital in South Africa **Inclusion criteria:** Adult daily smokers of at least 10 cpd **Exclusion criteria:** **H**istory of lung disease
Participants	Total N: 15, mean age 38 years, smoked 20 cpd (range 10 - 30), for an average of 17 years (range 5 - 27) Total N: 13 completed the study (5 women)
Interventions	Participants were asked to use an EC only for 2 weeks (i.e. no cigarettes) EC: 'Twisp eGo' cartridge 0.8 ml containing 0.0144 mg of nicotine
Outcomes	The following measurements were taken at baseline and 2-week follow-up: 1. Blood pressure and pulse 2. Arterial and venous COHb and blood oxygen saturation
Notes	Drop-outs (N = 2) were due to illness (headache and fever) and undertaking a military course associated with high stress and exposure to others smoking, making it difficult to abstain from cigarettes The paper states that the EC cartridge contained 0.8 ml of solution with 0.0144 mg of nicotine. This would be an unusually low concentration of nicotine and we have assumed an error in units where milligrams should have been grams (0.0144 grams of nicotine would make the concentration 18mg/ml)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	Prospective cohort
Allocation concealment (selection bias)	High risk	Not randomized
Blinding of participants and personnel (performance bias) All outcomes	High risk	No blinding
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Biochemically validated
Incomplete outcome data (attrition bias) All outcomes	Low risk	2/15 lost to follow-up
Selective reporting (reporting bias)	Unclear risk	Unable to determine prespecified outcomes
Other bias	Unclear risk	None noted

AE: adverse event

BMI: body mass index
CO: carbon monoxide
cpd: cigarettes per day
EC: electronic cigarette
FTND: Fagerström Test for Nicotine Dependence
IQR: interquartile range
ITT: intention-to-treat
LTFU: lost to follow-up
NEC: nicotine electronic cigarette
NRT: nicotine replacement therapy
PEC: placebo electronic cigarette
SAE: serious adverse event
SD: standard deviation
TQD: target quit date

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Adkison 2013	Although this study utilises a prospective cohort design, no data on EC use were collected at baseline, with EC use data only being available at follow-up
Battista 2013	Short-term EC use only
Brown 2014a	Cross-sectional survey.
Bullen 2010	Short-term EC use only
Chorti 2012	Short-term EC use only
Czogala 2012	Short-term EC use only
Dawkins 2012	Short-term EC use only
Dawkins 2013a	Short-term EC use only
Dawkins 2014	Short-term EC use only
Douptcheva 2013	Longitudinal study, but no data are reported for smoking cessation or reduction or for adverse events
Dutra 2014	Cross-sectional survey
Eissenberg 2010	Short-term EC use only
Farsalinos 2012	Short-term EC use only
Farsalinos 2013a	Included people that had already stopped smoking conventional cigarettes

(*Continued*)

Farsalinos 2013b	Short-term EC use only
Farsalinos 2013c	Short-term EC use only
Farsalinos 2013d	Short-term EC use only
Flouris 2012	Short-term EC use only
Flouris 2013	Short-term EC use only
Kasza 2013	Longitudinal study, but no data are reported for smoking cessation or reduction or for adverse events
Kouretas 2012	Short-term EC use only
Lee 2014	Cross-sectional survey
Marini 2014	Short-term EC use only
Palamidas 2014	Short-term EC use only
Pearson 2012	Longitudinal study, but no data are reported for smoking cessation or reduction or for adverse events
Pokhrel 2013	Cross-sectional survey
Popova 2013	Cross-sectional survey
Schober 2014	Short-term EC use only
Siegel 2011	Retrospective survey of 222 EC users that responded to a survey sent to 5000 new users of the 'Blu' EC. Likely to be a self-selected sample
Tsikrika 2014	Short-term EC use only
Tzatzarakis 2013	Short-term EC use only
Vakali 2014	Short-term EC use only
Vansickel 2010	Short-term EC use only
Vansickel 2012	Short-term EC use only
Vansickel 2013	Short-term EC use only
Vardavas 2012	Short-term EC use only
Vickerman 2013	Cross-sectional survey

(*Continued*)

Wagener 2014	EC use for up to 1 week, but does not report on any adverse events

Characteristics of ongoing studies *[ordered by study ID]*

Caponnetto 2014

Trial name or title	Smoking cessation and reduction In schizophrenia (the SCARIS study)
Methods	3-arm prospective 12m randomized controlled trial investigating efficacy and safety of EC Setting: psychiatric and smoking cessation centres, Italy Recruitment: local newspapers and radio/television advertisements
Participants	153 participants, schizophrenic in stable phase of illness, smoked at least 10 cpd over previous 5 years, aged 18 - 65, in good general health, not currently attempting to quit smoke or wishing to do so in next 6m Excluded if: use smokeless tobacco or NRT; pregnant or breastfeeding; current or recent (1 yr) history of drug or alcohol abuse; other significant co-morbidities
Interventions	12 week supply of: 1) EC, high nicotine (24 mg) 2) EC, no nicotine (0 mg, with tobacco aroma) 3) PAIPO nicotine-free inhalator
Outcomes	Follow-up visits at 4, 8, 12, 24 and 52 weeks Outcome measures: • Smoking cessation • Smoking reduction (≥ 50% from baseline) • Adverse events • Quality of life • Neurocognitive functioning • Participant perceptions and satisfactions with products
Starting date	September 2014
Contact information	Pasquale Caponnetto, p.caponnetto@unict.it
Notes	

Manzoli 2013

Trial name or title	The efficacy and safety of electronic cigarettes: a 5-year follow-up study
Methods	Multicentre prospective cohort study Setting: Italy Recruitment: newspaper and Internet advertisements, investigator contact at shops, GP volunteers

Manzoli 2013 (*Continued*)

Participants	Maximum 1500 participants (500 EC users at baseline, 500 smokers who do not use EC at baseline, and 500 dual users) Inclusion criteria: resident in Italy, aged 30 - 75, either: EC user for at least 6m inhaling at least 50 puffs/day; smokers of at least 1 cpd for at least 6m; smoker of both EC and traditional cigarettes (at least 1 cigarette/day) for at least 6m Exclusion criteria: illicit drug use; pregnant or breastfeeding; major depression or other psychiatric conditions; severe allergies; antihypertensive medication; angina pectoris; past episodes of selected smoking-related major diseases (see outcomes below)
Interventions	Compare health effects of EC vs traditional vs mixed cigarette smoking
Outcomes	Questionnaires at baseline and at 6, 12, 24, 36 and 60m Outcomes: • Cessation (portable CO monitors): percentage of subjects that were current or former smokers reporting sustained abstinence from traditional cigarette smoking at all time points, defined as complete abstinence (not even a puff) • Reduction: average in difference in self-reported number of traditional cpd at baseline • Adherence to ECs • Self-reported adverse events • Quality of life • Time to hospital admission for CVD, COPD, cancers of the lung, oesophagus, larynx, oral cavity, bladder, pancreas, kidney, stomach, cervix, and myeloid leukaemia
Starting date	June 2013
Contact information	Lamberto Manzoli, lmazoli@post.harvard.edu
Notes	

NCT01194583

Trial name or title	Efficacy and safety of an electronic nicotine delivery device (e-cigarette) without nicotine cartridges
Methods	Prospective cohort study Setting: community, Italy
Participants	100 "regular smokers" Inclusion criteria: healthy smokers unwilling to quit, 18 - 60 years old, at least 15 cpd for previous 5 years, CO at least 15 ppm, FTND at least 5 Exclusion criteria: alcohol and illicit drug use, breastfeeding or pregnancy, current attempts to quit smoking, previous experience with ECs
Interventions	Categoria EC, "NO nicotine" cartridges, provided for up to 24 wks
Outcomes	Study visits at 2, 4, 6, 8, 10, 12 and 24 wks Outcome measures: • Sustained 50% reduction in cpd • Sustained abstinence at 12 wks (not even a puff for 14 days prior to study visit, validated via exhaled

NCT01194583 (*Continued*)

	CO) • Sustained 80% reduction in cpd • Withdrawal suppression • Cravings reduction • Adverse events
Starting date	April 2010
Contact information	Riccardo Polosa, Universita degli Studi di Catania
Notes	

NCT01842828

Trial name or title	Spain-UK-Czech E-cigarette Study (SUKCES)
Methods	Randomized controlled trial, open-label pilot study Setting: smoking cessation clinics in London, Madrid and Prague Recuitment: via smoking cessation clinics
Participants	220 smokers seeking help to quit Inclusion criteria: 18 or older,want help to quit Exclusion criteria: pregnant or breastfeeding; enrolled in other research; currently using EC
Interventions	1) standard care plus 4 wks EC supply 2) standard care only
Outcomes	• CO-validated continuous abstinence at 4 and 24 wks post-TQD • Withdrawal symptoms at 1 and 4 wks post-TQD • EC use • EC taste and satisfaction compared to conventional cigarettes • Adverse events
Starting date	December 2013
Contact information	Peter Hajek, p.hajek@qmul.ac.uk
Notes	

NCT01989923

Trial name or title	Smoking cessation in women with gynaecological conditions
Methods	Randomized controlled trial, open-label feasibility study Setting: hospital clinic, USA Recruitment: in clinic

NCT01989923 (*Continued*)

Participants	30 women smokers with cervical dysplasia Inclusion criteria: women smokers of at least 10 cpd over past year, diagnosis of cervical dysplasia, cervical cancer, and lower genital tract dysplasia and cancer, aged 18 - 65 Exclusion criteria: previous diagnoses or treatment for cancer (except for non-melanoma skin cancer); stroke, heart disease, heart attack, or irregular heart beat; pregnancy and lactation; plan to continue to use other nicotine as well as study products; uncontrolled hypertension; using other stop-smoking medication; taking prescription medicine for depression or asthma
Interventions	1) NRT patch (21 mg for first 3 wks, 14 mg for second 3 wks) plus nicotine gum (2 mg) or lozenges (2 mg) for 6 wks 2) E-cig device ('Blu' Cig) with refills to last 6 wks, number provided based on packs smoked per day x 1.5. Strength of EC reduced at 3 wks Both groups receive identical cessation counselling
Outcomes	At 6 and 12 wks via survey: • Cpd • Point prevalence abstinence at 7 and 30 days • Smoking cessation • Participants' attitudes and beliefs towards treatments • Adherence
Starting date	June 2013
Contact information	Laura A Beebe, laura-beebe@ouhsc.edu
Notes	

NCT02004171

Trial name or title	Electronic cigarettes or nicotine inhaler for smoking cessation
Methods	Randomized controlled trial, open-label safety/efficacy study Setting and recruitment not specified, USA
Participants	40 participants Inclusion criteria: 18 - 60 years old, meet DSM-IV criteria for nicotine dependence, seeking treatment for smoking cessation, smoking at least 15 cpd Exclusion criteria: DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder; current diagnosis of major depressive disorder; current diagnosis for other psychiatric disorders that may require intervention over course of study; receiving treatment for nicotine dependence; pregnancy, lactation, or chance of pregnancy; unstable medical condition; substance abuse diagnosis; use of cannabis or alcohol on more than 20 days in past 30 days; suicide risk
Interventions	4 weeks: 1) electronic cigarettes (2nd generation) with 24 mg nicotine cartridges, 1 - 2 cartridges daily 2) nicotine inhaler with 10 mg cartridges, max 16 cartridges per day

NCT02004171 (*Continued*)

Outcomes	Over 4 weeks: • cpd • Withdrawal • Benefits from smoking cessation (breathing, sense of taste and smell, physical fitness) • Adverse events • BMI
Starting date	December 2013
Contact information	Barney Vaughan, vaughan@nyspi.columbia.edu
Notes	

NCT02029196

Trial name or title	A study to evaluate the safety profile of an e-vapour product
Methods	Randomized, open-label, multi-centre trial
Participants	420 participants Inclusion criteria: age 21 - 65 years, BMI 18 - 35kg/m², established smokers (smoking 5 - 30 cpd for at least 1 year), not wanting to quit Exclusion Criteria: use of NRT within 14 days, blood donation in previous 12 months, history of drug or alcohol abuse, HIV or hepatitis positive, medically unwell, pregnant women
Interventions	12 weeks: Experimental: Participants who switch from using conventional cigarettes to using an e-vapour product (EVP) . No further information available about this product Control: Participants who continue smoking their usual conventional cigarette
Outcomes	Over 12 weeks: Primary • Vital signs • ECG • Lung function testing • Clinical laboratory parameters Secondary • Craving and withdrawal symptoms • Carboxyhaemoglobin • High-density lipoprotein cholesterol
Starting date	December 2013
Contact information	Robert Turner, robert.turner˙cain@covance.com
Notes	Sponsor: Imperial Tobacco Group PLC

NCT02124187

Trial name or title	Smoking cessation and reduction in depression (SCARID)
Methods	3-arm prospective 12m randomized controlled trial investigating efficacy and safety of ECs
Participants	129 participants Inclusion Criteria: diagnosis of major depressive disorder (MDD) (according to DSM-5 criteria), smoke ≥ 10 cpd (for at least the past 5 years), age 18 - 65 years, in good general health, unwilling to quit smoking in the next 30 days Exclusion Criteria: use of smokeless tobacco or NRT or other smoking cessation therapies, pregnancy or breastfeeding, current or recent (< 1 yr) past history of alcohol or drug abuse or both, active suicidal intention, other significant co-morbidities according to the Investigator's clinical assessment (e.g. cancer, acute myocardial infarction, unstable angina, severe cardiac arrhythmia, recent cerebrovascular incident, or severe atherosclerosis)
Interventions	12-week supply of: 1. EC 24 mg nicotine 2. EC 0 mg nicotine 3. Nicotine-free inhalator
Outcomes	Follow-up visits at 4, 8, 12, 24 and 52 wks Outcome measures: • Smoking cessation • Smoking reduction (≥ 50% from baseline) • Adverse events • Quality of life • Neurocognitive functioning • Participant perceptions and satisfactions with products
Starting date	February 2015
Contact information	Pasquale Caponnetto p.caponnetto@unict.it
Notes	

NCT02143310

Trial name or title	A study to evaluate the safety of electronic vapour products for 2 years
Methods	Open-label, singe-group assignment, multi-centre trial
Participants	420 participants Inclusion criteria: participated in NCT02029196, age 21 - 65 years, BMI 18 - 35kg/m2, established smokers (smoking 5 - 30 cpd for at least 1 year) not wanting to quit, willingness to use the electronic vaporised product for 2 years, no clinically significant abnormalities during the prior trial Exclusion criteria: use of NRT within 14 days, blood donation in previous 12 months, history of drug or alcohol abuse, HIV or hepatitis positive, medically unwell, pregnant women
Interventions	Use of e-vapour product (EVP) for two years.

NCT02143310 (*Continued*)

Outcomes	Follow-up visits at 1, 2, 3, 6, 9, 12, 15, 18, 21, and 24 months Primary • Change from baseline (BL) in blood pressure • Change from BL in ECG • Change from BL in lung function tests • Change from BL in clinical laboratory parameters Secondary • Change from BL in craving and withdrawal symptoms • Change from BL in biomarkers of exposure • Change from BL in biomarkers of effect
Starting date	May 2014
Contact information	Robert Turner, robert.turner˙cain@covance.com
Notes	

BMI: body mass index
COPD: chronic obstructive pulmonary disease
cpd: cigarettes per day
CVD: cardiovascular disease
EC: electronic cigarette
ECG: electrocardiogram
NRT: nicotine replacement therapy
wk: week
yr: year

DATA AND ANALYSES

Comparison 1. Smoking cessation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nicotine EC versus placebo EC	2	662	Risk Ratio (M-H, Fixed, 95% CI)	2.29 [1.05, 4.96]
2 Nicotine EC versus nicotine replacement therapy	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 2. Smoking reduction

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Nicotine EC versus placebo EC (quitters excluded)	2	612	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.02, 1.68]
2 Nicotine EC versus nicotine replacement therapy (quitters excluded)	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Comparison 3. Adverse Events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Proportion of participants reporting adverse events: Nicotine EC versus placebo EC	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected
2 Proportion of participants reporting adverse events: nicotine EC versus nicotine replacement therapy	1		Risk Ratio (M-H, Fixed, 95% CI)	Totals not selected

Analysis 1.1. Comparison 1 Smoking cessation, Outcome 1 Nicotine EC versus placebo EC.

Review: Electronic cigarettes for smoking cessation and reduction

Comparison: 1 Smoking cessation

Outcome: 1 Nicotine EC versus placebo EC

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bullen 2013	21/289	3/73		47.3 %	1.77 [0.54, 5.77]
Caponnetto 2013a	22/200	4/100		52.7 %	2.75 [0.97, 7.76]
Total (95% CI)	**489**	**173**		**100.0 %**	**2.29 [1.05, 4.96]**

Total events: 43 (Experimental), 7 (Control)

Heterogeneity: $Chi^2 = 0.30$, df = 1 (P = 0.58); $I^2 = 0.0\%$

Test for overall effect: Z = 2.09 (P = 0.037)

Test for subgroup differences: Not applicable

Analysis 1.2. Comparison 1 Smoking cessation, Outcome 2 Nicotine EC versus nicotine replacement therapy.

Review: Electronic cigarettes for smoking cessation and reduction

Comparison: 1 Smoking cessation

Outcome: 2 Nicotine EC versus nicotine replacement therapy

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Bullen 2013	21/289	17/295		1.26 [0.68, 2.34]

Analysis 2.1. Comparison 2 Smoking reduction, Outcome 1 Nicotine EC versus placebo EC (quitters excluded).

Review: Electronic cigarettes for smoking cessation and reduction

Comparison: 2 Smoking reduction

Outcome: 1 Nicotine EC versus placebo EC (quitters excluded)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Bullen 2013	165/268	33/70		77.0 %	1.31 [1.00, 1.70]
Caponnetto 2013a	29/178	12/96		23.0 %	1.30 [0.70, 2.44]
Total (95% CI)	**446**	**166**		**100.0 %**	**1.31 [1.02, 1.68]**

Total events: 194 (Experimental), 45 (Control)

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 2.09 (P = 0.037)

Test for subgroup differences: Not applicable

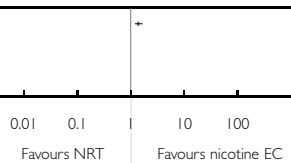
Analysis 2.2. Comparison 2 Smoking reduction, Outcome 2 Nicotine EC versus nicotine replacement therapy (quitters excluded).

Review: Electronic cigarettes for smoking cessation and reduction

Comparison: 2 Smoking reduction

Outcome: 2 Nicotine EC versus nicotine replacement therapy (quitters excluded)

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Bullen 2013	165/268	121/278		1.41 [1.20, 1.67]



Analysis 3.1. Comparison 3 Adverse Events, Outcome 1 Proportion of participants reporting adverse events: Nicotine EC versus placebo EC.

Review: Electronic cigarettes for smoking cessation and reduction

Comparison: 3 Adverse Events

Outcome: 1 Proportion of participants reporting adverse events: Nicotine EC versus placebo EC

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Bullen 2013	107/241	26/57		0.97 [0.71, 1.34]

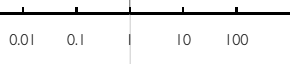
Analysis 3.2. Comparison 3 Adverse Events, Outcome 2 Proportion of participants reporting adverse events: nicotine EC versus nicotine replacement therapy.

Review: Electronic cigarettes for smoking cessation and reduction

Comparison: 3 Adverse Events

Outcome: 2 Proportion of participants reporting adverse events: nicotine EC versus nicotine replacement therapy

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Risk Ratio M-H,Fixed,95% CI
Bullen 2013	107/241	96/215		0.99 [0.81, 1.22]



ADDITIONAL TABLES

Table 1. Summary of proportion of participants abstinent from smoking at follow-up: cohort studies

Study	Smokers motivated or unmotivated to quit?	Intervention vs relevant Control	% abstinent				
Cohort studies			**6 month**	**12 months**	**18 months**	**24 months**	**Notes**
Caponnetto 2013b	Unmotivated to quit	Nicotine EC		14% (2/14)			
Ely 2013	Motivated to quit	Nicotine EC[1]	44% (21/48)				
Polosa 2011	Unmotivated to quit	Nicotine EC	23% (9/40)		15% (6/40)	13% (5/40)	
Cohort studies not allowing inclusion of non-responders							
Etter 2014	Not defined	Daily EC users at baseline		46% (16/35)			Response rate: 47% (367/773) completed follow-up survey
Grana 2014b	Not defined	Used EC in the past 30 days (even once) at baseline		10% (9/88)			Response rate: 81% completed follow-up Abtsinence rate was 14% (119/861) in non-EC users
Choi 2014	Not defined	Used EC for ≥ 1 day in the past 30 days at baseline		11%			Response rate: unknown Abstinence rate was 17% in non-EC users

[1] All participants (N = 48) used an EC, but 16 also used bupropion and 2 used varenicline

Table 2. Summary of proportion of participants achieving a ≥ 50% reduction of baseline cigarette consumption: cohort studies

Study	Smokers motivated or unmotivated to quit?	Intervention vs. Control	% reduced by ≥ 50% of baseline cigarette consumption			
			6 month	12 months	18 months	24 months
Caponnetto 2013b	Unmotivated to quit	Nicotine EC		50% (7/14)		
Ely 2013	Motivated to quit	Nicotine EC[1]	27% (13/48)			
Polosa 2011	Unmotivated to quit	Nicotine EC	33% (13/40)		28% (11/40)	28% (11/40)

[1] All participants (N = 48) used an EC, but 16 also used bupropion and 2 used varenicline

APPENDICES

Appendix 1. MEDLINE search strategy

1. e-cig$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
2. electr$ cigar$.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
3. electronic nicotine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier]
4. 1 OR 2 OR 3

CONTRIBUTIONS OF AUTHORS

All authors contributed to the writing of this review.

JHB and HM extracted data, with discrepancies and disagreements referred to PH.

As principal investigator of one of the included trials, CB was not involved with data extraction or assessment of study quality.

DECLARATIONS OF INTEREST

Within the last three years HM has undertaken educational sessions sponsored by Pfizer and Johnson & Johnson, manufacturers of smoking cessation medications.

Within the last three years PH has provided consultancy to GSK, Pfizer, and Johnson & Johnson, manufacturers of smoking cessation medications.

Due to these two interests, this review is not compliant with the Cochrane commercial sponsorship policy, as updated in 2014. At the time the protocol was published it was compliant.

Two authors (HM, CB) have additional declarations:

CB and HM were investigators on a study of ECs from an EC manufacturer (Ruyan Group, Beijing and Hong Kong). Ruyan supplied the ECs used in the trial and contracted with Health NZ Ltd. to undertake the study. Health New Zealand Ltd funded The University of Auckland to conduct the trial, independently of Ruyan Group (Holdings) Ltd. The trial design conduct, analysis and interpretation of results were conducted independently of the sponsors.

CB and HM were investigators on the ASCEND EC trial funded by the Health Research Council of New Zealand that used product supplied at no charge from PGM international, a retailer of ECs.

JHB has no conflicts of interest to declare.

SOURCES OF SUPPORT

Internal sources

- Queen Mary University of London, UK.

provides salary, office space and library resources for HM and PH

- The University of Auckland, New Zealand.

provides salary, office space and library resources for CB

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Originally, the protocol did not specify a minimum follow-up period for data on adverse events. The Methods section has been changed to clarify that we will exclude follow-up data at less than a week.

INDEX TERMS

Medical Subject Headings (MeSH)

*Electronic Cigarettes [adverse effects; instrumentation]; Cohort Studies; Nicotine [administration & dosage]; Nicotinic Agonists [administration & dosage]; Publication Bias; Randomized Controlled Trials as Topic; Smoking [epidemiology; *prevention & control]; Smoking Cessation [*methods]; Tobacco Use Cessation Products

MeSH check words

Humans; Middle Aged