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**WILEY**

[Intervention Review]

# Electronic cigarettes for smoking cessation

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## ABSTRACT

### Background

Electronic cigarettes (ECs) are handheld electronic vaping devices which produce an aerosol formed by heating an e-liquid. Some people who smoke use ECs to stop or reduce smoking, but some organizations, advocacy groups and policymakers have discouraged this, citing lack of evidence of efficacy and safety. People who smoke, healthcare providers and regulators want to know if ECs can help people quit and if they are safe to use for this purpose. This is an update conducted as part of a living systematic review.

### Objectives

To examine the effectiveness, tolerability, and safety of using electronic cigarettes (ECs) to help people who smoke tobacco achieve long-term smoking abstinence.

### Search methods

We searched the Cochrane Tobacco Addiction Group's Specialized Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase, and PsycINFO to 1 May 2021, and reference-checked and contacted study authors. We screened abstracts from the Society for Research on Nicotine and Tobacco (SRNT) 2021 Annual Meeting.

### Selection criteria

We included randomized controlled trials (RCTs) and randomized cross-over trials, in which people who smoke were randomized to an EC or control condition. We also included uncontrolled intervention studies in which all participants received an EC intervention. Studies had to report abstinence from cigarettes at six months or longer or data on safety markers at one week or longer, or both.

### Data collection and analysis

We followed standard Cochrane methods for screening and data extraction. Our primary outcome measures were abstinence from smoking after at least six months follow-up, adverse events (AEs), and serious adverse events (SAEs). Secondary outcomes included the proportion of people still using study product (EC or pharmacotherapy) at six or more months after randomization or starting EC use, changes in carbon monoxide (CO), blood pressure (BP), heart rate, arterial oxygen saturation, lung function, and levels of carcinogens or toxicants or both. We used a fixed-effect Mantel-Haenszel model to calculate risk ratios (RRs) with a 95% confidence interval (CI) for dichotomous outcomes. For continuous outcomes, we calculated mean differences. Where appropriate, we pooled data in meta-analyses.

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## Main results

We included 61 completed studies, representing 16,759 participants, of which 34 were RCTs. Five of the 61 included studies were new to this review update. Of the included studies, we rated seven (all contributing to our main comparisons) at low risk of bias overall, 42 at high risk overall (including all non-randomized studies), and the remainder at unclear risk.

There was moderate-certainty evidence, limited by imprecision, that quit rates were higher in people randomized to nicotine EC than in those randomized to nicotine replacement therapy (NRT) (risk ratio (RR) 1.53, 95% confidence interval (CI) 1.21 to 1.93;  $I^2 = 0\%$ ; 4 studies, 1924 participants). In absolute terms, this might translate to an additional three quitters per 100 (95% CI 1 to 6). There was low-certainty evidence (limited by very serious imprecision) that the rate of occurrence of AEs was similar (RR 0.98, 95% CI 0.80 to 1.19;  $I^2 = 0\%$ ; 2 studies, 485 participants). SAEs were rare, but there was insufficient evidence to determine whether rates differed between groups due to very serious imprecision (RR 1.30, 95% CI 0.89 to 1.90;  $I^2 = 0\%$ ; 4 studies, 1424 participants).

There was moderate-certainty evidence, again limited by imprecision, that quit rates were higher in people randomized to nicotine EC than to non-nicotine EC (RR 1.94, 95% CI 1.21 to 3.13;  $I^2 = 0\%$ ; 5 studies, 1447 participants). In absolute terms, this might lead to an additional seven quitters per 100 (95% CI 2 to 16). There was moderate-certainty evidence of no difference in the rate of AEs between these groups (RR 1.01, 95% CI 0.91 to 1.11;  $I^2 = 0\%$ ; 3 studies, 601 participants). There was insufficient evidence to determine whether rates of SAEs differed between groups, due to very serious imprecision (RR 1.06, 95% CI 0.47 to 2.38;  $I^2 = 0\%$ ; 5 studies, 792 participants).

Compared to behavioural support only/no support, quit rates were higher for participants randomized to nicotine EC (RR 2.61, 95% CI 1.44 to 4.74;  $I^2 = 0\%$ ; 6 studies, 2886 participants). In absolute terms this represents an additional six quitters per 100 (95% CI 2 to 15). However, this finding was of very low certainty, due to issues with imprecision and risk of bias. There was some evidence that non-serious AEs were more common in people randomized to nicotine EC (RR 1.22, 95% CI 1.12 to 1.32;  $I^2 = 41\%$ , low certainty; 4 studies, 765 participants), and again, insufficient evidence to determine whether rates of SAEs differed between groups (RR 1.51, 95% CI 0.70 to 3.24;  $I^2 = 0\%$ ; 7 studies, 1303 participants).

Data from non-randomized studies were consistent with RCT data. The most commonly reported AEs were throat/mouth irritation, headache, cough, and nausea, which tended to dissipate with continued use. Very few studies reported data on other outcomes or comparisons, hence evidence for these is limited, with CIs often encompassing clinically significant harm and benefit.

## Authors' conclusions

There is moderate-certainty evidence that ECs with nicotine increase quit rates compared to NRT and compared to ECs without nicotine. Evidence comparing nicotine EC with usual care/no treatment also suggests benefit, but is less certain. More studies are needed to confirm the effect size. Confidence intervals were for the most part wide for data on AEs, SAEs and other safety markers, with no difference in AEs between nicotine and non-nicotine ECs. Overall incidence of SAEs was low across all study arms. We did not detect evidence of harm from nicotine EC, but longest follow-up was two years and the number of studies was small.

The main limitation of the evidence base remains imprecision due to the small number of RCTs, often with low event rates, but further RCTs are underway. To ensure the review continues to provide up-to-date information to decision-makers, this review is now a living systematic review. We run searches monthly, with the review updated when relevant new evidence becomes available. Please refer to the *Cochrane Database of Systematic Reviews* for the review's current status.

## PLAIN LANGUAGE SUMMARY

### Can electronic cigarettes help people stop smoking, and do they have any unwanted effects when used for this purpose?

#### What are electronic cigarettes?

Electronic cigarettes (e-cigarettes) are handheld devices that work by heating a liquid that usually contains nicotine and flavourings. E-cigarettes allow you to inhale nicotine in a vapour rather than smoke. Because they do not burn tobacco, e-cigarettes do not expose users to the same levels of chemicals that can cause diseases in people who smoke conventional cigarettes.

Using an e-cigarette is commonly known as 'vaping'. Many people use e-cigarettes to help them to stop smoking tobacco. In this review we focus primarily on nicotine e-cigarettes.

#### Why we did this Cochrane Review

Stopping smoking lowers your risk of getting lung cancer, heart attacks and many other diseases. Many people find it difficult to stop smoking. We wanted to find out if using e-cigarettes could help people to stop smoking, and if people using them for this purpose experience any unwanted effects.

#### What did we do?

We searched for studies that looked at the use of e-cigarettes to help people stop smoking.

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We looked for randomized controlled trials, in which the treatments people received were decided at random. This type of study usually gives the most reliable evidence about the effects of a treatment. We also looked for studies in which everyone received an e-cigarette treatment.

We were interested in finding out:

- how many people stopped smoking for at least six months; and
- how many people had unwanted effects, reported on after at least one week of use.

**Search date:** We included evidence published up to 1st May 2021.

### What we found

We found 61 studies in 16,759 adults who smoked. The studies compared e-cigarettes with:

- nicotine replacement therapy, such as patches or gum;
- varenicline (a medicine to help people stop smoking);
- nicotine-free e-cigarettes;
- other types of nicotine-containing e-cigarettes (e.g. pod devices, newer devices);
- behavioural support, such as advice or counselling; or
- no support for stopping smoking.

Most studies took place in the USA (26 studies), the UK (11), and Italy (7).

### What are the results of our review?

More people probably stop smoking for at least six months using nicotine e-cigarettes than using nicotine replacement therapy (4 studies, 1924 people), or nicotine-free e-cigarettes (5 studies, 1447 people).

Nicotine e-cigarettes may help more people to stop smoking than no support or behavioural support only (6 studies, 2886 people).

For every 100 people using nicotine e-cigarettes to stop smoking, 9 to 14 might successfully stop, compared with only 6 of 100 people using nicotine-replacement therapy, 7 of 100 using nicotine-free e-cigarettes, or four of 100 people having no support or behavioural support only.

We are uncertain if there is a difference between how many unwanted effects occur using nicotine e-cigarettes compared with nicotine replacement therapy, no support or behavioural support only. There was some evidence that non-serious unwanted effects were more common in groups receiving nicotine e-cigarettes compared to no support or behavioural support only. Similar low numbers of unwanted effects, including serious unwanted effects, were reported for other comparisons. There is probably no difference in how many non-serious unwanted effects occur in people using nicotine e-cigarettes compared to non-nicotine e-cigarettes.

The unwanted effects reported most often with nicotine e-cigarettes were throat or mouth irritation, headache, cough and feeling sick. These effects reduced over time as people continued using nicotine e-cigarettes.

### How reliable are these results?

Our results are based on a small number of studies, and in some the data varied widely.

We are moderately confident that nicotine e-cigarettes help more people to stop smoking than nicotine replacement therapy or nicotine-free e-cigarettes. More studies are still needed to confirm this.

Studies comparing nicotine e-cigarettes with behavioural or no support also showed higher quit rates in people using nicotine e-cigarettes, but provide less certain data because of issues with study design.

Most of our results for the unwanted effects may change when more evidence becomes available.

### Key messages

Nicotine e-cigarettes probably do help people to stop smoking for at least six months. They probably work better than nicotine replacement therapy and nicotine-free e-cigarettes.

They may work better than no support, or behavioural support alone, and they may not be associated with serious unwanted effects.

However, we need more evidence to be confident about the effects of e-cigarettes, particularly the effects of newer types of e-cigarettes that have better nicotine delivery than older types of e-cigarettes.