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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. People who smoke report using ECs to stop or reduce smoking, but some organisations, 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 review is an update of a review first published in 2014.

### Objectives

To evaluate the effect and safety of using electronic cigarettes (ECs) to help people who smoke 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 for relevant records to January 2020, together with reference-checking and contact with study authors.

### 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. To be included, studies had to report abstinence from cigarettes at six months or longer and/or data on adverse events (AEs) or other markers of safety at one week or longer.

### 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, AEs, and serious adverse events (SAEs). Secondary outcomes included changes in carbon monoxide, blood pressure, heart rate, blood oxygen saturation, lung function, and levels of known carcinogens/toxicants. We used a fixed-effect Mantel-Haenszel model to calculate the risk ratio (RR) with a 95% confidence interval (CI) for dichotomous outcomes. For continuous outcomes, we calculated mean differences. Where appropriate, we pooled data from these studies in meta-analyses.

## Main results

We include 50 completed studies, representing 12,430 participants, of which 26 are RCTs. Thirty-five of the 50 included studies are new to this review update. Of the included studies, we rated four (all which contribute to our main comparisons) at low risk of bias overall, 37 at high risk overall (including the 24 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) 1.69, 95% confidence interval (CI) 1.25 to 2.27;  $I^2 = 0\%$ ; 3 studies, 1498 participants). In absolute terms, this might translate to an additional four successful quitters per 100 (95% CI 2 to 8). There was low-certainty evidence (limited by very serious imprecision) of no difference in the rate of adverse events (AEs) (RR 0.98, 95% CI 0.80 to 1.19;  $I^2 = 0\%$ ; 2 studies, 485 participants). SAEs occurred rarely, with no evidence that their frequency differed between nicotine EC and NRT, but very serious imprecision led to low certainty in this finding (RR 1.37, 95% CI 0.77 to 2.41;  $I^2 = n/a$ ; 2 studies, 727 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 1.71, 95% CI 1.00 to 2.92;  $I^2 = 0\%$ ; 3 studies, 802 participants). In absolute terms, this might again lead to an additional four successful quitters per 100 (95% CI 0 to 12). These trials used EC with relatively low nicotine delivery. There was low-certainty evidence, limited by very serious imprecision, that there was no difference in the rate of AEs between these groups (RR 1.00, 95% CI 0.73 to 1.36;  $I^2 = 0\%$ ; 2 studies, 346 participants). There was insufficient evidence to determine whether rates of SAEs differed between groups, due to very serious imprecision (RR 0.25, 95% CI 0.03 to 2.19;  $I^2 = n/a$ ; 4 studies, 494 participants).

Compared to behavioural support only/no support, quit rates were higher for participants randomized to nicotine EC (RR 2.50, 95% CI 1.24 to 5.04;  $I^2 = 0\%$ ; 4 studies, 2312 participants). In absolute terms this represents an increase of six per 100 (95% CI 1 to 14). However, this finding was very low-certainty, due to issues with imprecision and risk of bias. There was no evidence that the rate of SAEs varied, but some evidence that non-serious AEs were more common in people randomized to nicotine EC (AEs: RR 1.17, 95% CI 1.04 to 1.31;  $I^2 = 28\%$ ; 3 studies, 516 participants; SAEs: RR 1.33, 95% CI 0.25 to 6.96;  $I^2 = 17\%$ ; 5 studies, 842 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 over time with continued use. Very few studies reported data on other outcomes or comparisons and hence evidence for these is limited, with confidence intervals often encompassing clinically significant harm and benefit.

## Authors' conclusions

There is moderate-certainty evidence that ECs with nicotine increase quit rates compared to ECs without nicotine and compared to NRT. Evidence comparing nicotine EC with usual care/no treatment also suggests benefit, but is less certain. More studies are needed to confirm the degree of effect, particularly when using modern EC products. Confidence intervals were wide for data on AEs, SAEs and other safety markers. Overall incidence of SAEs was low across all study arms. We did not detect any clear evidence of harm from nicotine EC, but longest follow-up was two years and the overall 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. Further RCTs are underway. To ensure the review continues to provide up-to-date information for decision-makers, this review is now a living systematic review. We will run searches monthly from December 2020, with the review updated as 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, ECs do not expose users to the same levels of toxins that we know can cause smoking-related diseases in people who use conventional cigarettes.

Using an e-cigarette is known as 'vaping'. Many people use e-cigarettes to help them to stop smoking tobacco.

#### Why we did this Cochrane Review

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

#### What did we do?

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

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 any unwanted effects.

We included studies that reported on smoking habits for at least six months, or reported on unwanted effects for at least one week.

**Search date:** We included evidence published up to January 2020.

### What we found

We found 50 studies in 12,430 adults who smoked. The studies compared e-cigarettes with:

- nicotine replacement therapy, such as patches or gum;
- varenicline;
- nicotine-free e-cigarettes;
- behavioural support, such as advice or counselling; or
- no support, for stopping smoking.

Some studies also tested using NRT and e-cigarettes together.

The studies took place in the USA (21 studies), the UK (9), Italy (7), Australia (2), New Zealand (2), Greece (2), and one study each in Belgium, Canada, Poland, South Korea, South Africa, Switzerland and Turkey.

### 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 (3 studies; 1498 people), or nicotine-free e-cigarettes (3 studies; 802 people).

Nicotine e-cigarettes may help more people to stop smoking than no support or behavioural support only (4 studies; 2312 people).

For every 100 people using nicotine e-cigarettes to stop smoking, 10 might successfully stop, compared with only six of 100 people using nicotine-replacement therapy or 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 using nicotine-free e-cigarettes, nicotine replacement therapy, no support or behavioural support only. Similar low numbers of unwanted effects, including serious unwanted effects, were reported for all groups.

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 measured 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. However, these results might change if further evidence becomes available.

We are less confident about how nicotine e-cigarettes compare with no support, or behavioural support, to stop smoking.

Our results for the unwanted effects are likely to 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, reliable evidence to be confident about the effects of e-cigarettes, particularly the effects of newer types of e-cigarettes that have better nicotine delivery.