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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 by heating an e-liquid. Some people who smoke use ECs to stop or reduce smoking, although 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 smoking, and if they are safe to use for this purpose. This is a review 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 July 2022, and reference-checked and contacted 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. 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.

## Main results

We included 78 completed studies, representing 22,052 participants, of which 40 were RCTs. Seventeen of the 78 included studies were new to this review update. Of the included studies, we rated ten (all but one contributing to our main comparisons) at low risk of bias overall, 50 at high risk overall (including all non-randomized studies), and the remainder at unclear risk.

There was high certainty that quit rates were higher in people randomized to nicotine EC than in those randomized to nicotine replacement therapy (NRT) (RR 1.63, 95% CI 1.30 to 2.04;  $I^2 = 10\%$ ; 6 studies, 2378 participants). In absolute terms, this might translate to an additional four quitters per 100 (95% CI 2 to 6). There was moderate-certainty evidence (limited by imprecision) that the rate of occurrence of AEs was similar between groups (RR 1.02, 95% CI 0.88 to 1.19;  $I^2 = 0\%$ ; 4 studies, 1702 participants). SAEs were rare, but there was insufficient evidence to determine whether rates differed between groups due to very serious imprecision (RR 1.12, 95% CI 0.82 to 1.52;  $I^2 = 34\%$ ; 5 studies, 2411 participants).

There was moderate-certainty evidence, 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;  $I^2 = 0\%$ ; 5 studies, 1840 participants). There was insufficient evidence to determine whether rates of SAEs differed between groups, due to very serious imprecision (RR 1.00, 95% CI 0.56 to 1.79;  $I^2 = 0\%$ ; 8 studies, 1272 participants).

Compared to behavioural support only/no support, quit rates were higher for participants randomized to nicotine EC (RR 2.66, 95% CI 1.52 to 4.65;  $I^2 = 0\%$ ; 7 studies, 3126 participants). In absolute terms, this represents an additional two quitters per 100 (95% CI 1 to 3). 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 1.03, 95% CI 0.54 to 1.97;  $I^2 = 38\%$ ; 9 studies, 1993 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 EC 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 high-certainty evidence that ECs with nicotine increase quit rates compared to NRT and moderate-certainty evidence that they increase quit rates 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 nor between nicotine ECs and NRT. Overall incidence of SAEs was low across all study arms. We did not detect evidence of serious 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 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 e-cigarettes containing nicotine.

#### Why we did this Cochrane Review

Stopping smoking lowers your risk of 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.

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## 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 unwanted effects, reported on after at least one week of use.

**Search date:** We included evidence published up to 1st July 2022.

## What we found

We found 78 studies which included 22,052 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);
- e-cigarettes without nicotine;
- 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 (34 studies), the UK (16), and Italy (8).

## What are the results of our review?

People are more likely to stop smoking for at least six months using nicotine e-cigarettes than using nicotine replacement therapy (6 studies, 2378 people), or e-cigarettes without nicotine (5 studies, 1447 people).

Nicotine e-cigarettes may help more people to stop smoking than no support or behavioural support only (7 studies, 3126 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 e-cigarettes without nicotine, or 4 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. Low numbers of unwanted effects, including serious unwanted effects, were reported in studies comparing nicotine e-cigarettes to nicotine replacement therapy. There is probably no difference in how many non-serious unwanted effects occur in people using nicotine e-cigarettes compared to e-cigarettes without nicotine.

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 few studies for most outcomes, and for some outcomes, the data varied widely.

We found evidence that nicotine e-cigarettes help more people to stop smoking than nicotine replacement therapy. Nicotine e-cigarettes probably help more people to stop smoking than e-cigarettes without nicotine but 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 could change when more evidence becomes available.

## Key messages

Nicotine e-cigarettes can help people to stop smoking for at least six months. Evidence shows they work better than nicotine replacement therapy, and probably better than e-cigarettes without nicotine.

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

However, we still need more evidence, particularly about the effects of newer types of e-cigarettes that have better nicotine delivery than older types of e-cigarettes, as better nicotine delivery might help more people quit smoking.