



# A new Cochrane review on electronic cigarettes for smoking cessation: should we change our practice?

*To the Editor:*

In 2014, a Cochrane review concluded that there was evidence from two randomised controlled trials (RCTs) that electronic cigarettes help smokers to stop smoking long term. The confidence in the result was rated “low”. In 2016, the same conclusion was reached. In the recently published 2020 update [1], the authors write that they included 50 completed studies, representing 12 430 participants. When you read closer, the smoking cessation conclusions are based on 12 RCTs, and half of these were small studies. The authors judged only four of the studies to be at low risk of bias [2–5].

It was possible for the authors to compare e-cigarettes with nicotine with three existing evidence-based smoking cessation treatments (table 1).

Based on three trials, the authors concluded that there is moderate certainty evidence, limited by imprecision, that e-cigarettes with nicotine increase quit rates at 6 months or longer compared to nicotine replacement therapy (NRT). The other conclusion is that there is very low certainty evidence that e-cigarettes with nicotine increase quit rates compared to behavioural support alone/to no support. The effect of nicotine-containing e-cigarettes when added to NRT is unclear. One small varenicline trial has been performed and showed significantly better quit rates than e-cigarettes with nicotine, but the trial was rated as having a very high risk of bias.

The review has been systematic, and the meta-analyses have high quality. Two review authors have independently and systematically assessed the risks of bias for each study, and a conservative approach was used for missing data; all this is strength. The three principal investigators of included trials (and co-authors of the review) were, at least, not involved with data extraction or “risk of bias” assessments.

However, there are some concerns. The authors write that in two studies where e-cigarettes with nicotine was provided, nicotine levels were judged to be so low that they chose to include these studies as non-nicotine e-cigarette comparisons. This is a very unusual decision. One of the studies showed lower effect of e-cigarette use than of NRT use.

Behavioural support and no support were merged as one comparison group. This is also an unusual decision, as behavioural support has an evidence-based effect, while no support has no effect on smoking cessation; again, this decision would favour e-cigarettes.

An RCT compared free nicotine e-cigarettes with incentives; this is not mentioned. Redeemable deposits were significantly superior to e-cigarettes (odds ratio 2.9) [6].

The authors decided to include uncontrolled intervention studies because of the paucity of RCTs. These cohort studies were primarily used to investigate the safety of e-cigarette use. It is a good decision to supplement with longitudinal studies when there are few RCTs, but it is puzzling why authors decided not to include the many existing cohort studies from the general population. It is well-known that a selection occurs in clinical trials (inclusion of more resourceful persons with higher socioeconomic status and better health).

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**There are several concerns regarding the review. Contradicting results from cohort studies were not considered. Smoking cessation rates achieved with e-cigarettes are low. The harms of long-term e-cigarette use will outweigh the potential benefit.** <https://bit.ly/3khrzBZ>

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TABLE 1 Randomised controlled trials (RCTs) comparing nicotine-containing electronic cigarettes with nicotine replacement therapy (NRT), varenicline and behavioural support/counseling

Intervention	Comparison group	Number of RCTs included	Result	Certainty of evidence (GRADE)
E-cigarette with nicotine	NRT	3	E-cigarette with nicotine significantly better	Moderate
E-cigarette with nicotine	Varenicline	1	Varenicline significantly better	Not assessed
E-cigarette with nicotine	Behavioural support/no support	4	E-cigarette with nicotine significantly better	Very low
E-cigarette with nicotine	E-cigarette without nicotine	3	E-cigarette with nicotine significantly better	Moderate
E-cigarette with nicotine + NRT	E-cigarette without nicotine + NRT	2	E-cigarette with nicotine significantly better	Not assessed
E-cigarette with nicotine + NRT	NRT	1	No significant difference	Not assessed

A co-author of the review, C. Notley, was a speaker at the Global Forum on Nicotine, that facilitates a dialogue with the tobacco industry. L. Dawkins was chosen as reviewer of the Cochrane review. In previous publications she stated that she had a collaborative relationship with e-cigarette companies, had received funding to speak at research conferences and benefits in kind from e-cigarette companies [7, 8]. The Cochrane review states that she has not received any funds from e-cigarette companies in the past 4 years. A recent study found a strong association between tobacco- and e-cigarette industry-related conflict of interest and industry-favourable results [9].

The authors do not present a balanced scientific view in the review. As an example, the authors write that there is a concern that e-cigarettes may be a gateway to smoking initiation, but that there are limited data with which to support or refute this concern. However, there is substantial evidence that e-cigarettes are a gateway to smoking initiation [10, 11] and many newer longitudinal studies have confirmed this finding, also in the UK [12]. The same occurs when authors discuss dual use. Only studies where toxins were found to be reduced are mentioned, even though several other studies demonstrated that toxicant exposure was either not reduced or increased [13]. Results from population-based cohort studies showing that dual use might be more harmful than smoking alone are not mentioned [14, 15].

The major flaw of the review is that it does not address following facts:

- 1) Population-based cohort studies do not show a benefit of e-cigarette use on smoking cessation;
- 2) Many of those who use e-cigarettes for smoking cessation continue using them long-term; and
- 3) A large number of *in vitro*, animal, experimental human and population-based studies have shown negative health effects of e-cigarette use.

Before we recommend the use of e-cigarettes as a smoking cessation tool to the broad population, we need to know what happens when they are used in the population, not only in intervention studies (including a selected population advised by researchers/health professionals). It would have been highly relevant in this review to mention that many population-based longitudinal studies show no effect of e-cigarette use on long-term smoking cessation [16–18] and that some cohorts show an increased risk of relapse in e-cigarette users [19, 20].

It would also have been very relevant to mention that many of those who quit with e-cigarettes continue using e-cigarettes in the long term (80% after 1 year in the trial reported by HAJEK *et al.* [2]) [3, 21]. Smoking cessation medication is typically prescribed/recommended for 8–12 weeks, as we want to avoid adverse events. However, when it comes to e-cigarettes, people are just asked to switch and no stop-date for e-cigarette use is recommended; they are used as consumer products.

The Cochrane review also investigated the safety of e-cigarette use and the authors concluded that they “did not detect any clear evidence of harm from nicotine e-cigarettes, but the longest follow-up was 2 years”. It would have been more correct to write “6 months”, as most of the included studies had a follow-up of 6 months. Authors do not mention any of the hundreds of animal, human and *in vitro* studies indicating harmful effects of e-cigarette use [22–25]. This could be ignored in 2014 as our knowledge was sparse, but not in 2020. A recent review concluded that the current knowledge of these

effects is insufficient to determine whether the respiratory health effects of e-cigarettes are less than those of combustible tobacco products [24].

Should we change our practice based on this new Cochrane review?

It is noteworthy to look at the quit rates. The pragmatic RCTs showed that approximately 5–7% of the participants in the e-cigarette group were smoke-free after 6 months [3, 6, 21]. Clinic-based RCTs, offering e-cigarettes and behavioural therapy, achieved abstinence rates of 16–18% after 6 or 12 months [2, 26]. An evaluation of the UK's national smoking cessation clinics (before e-cigarettes were invented) showed validated quit rates of 15% at 1 year [27], which is comparable to the abstinence rate of 16% at 1 year in Danish national smoking cessation clinics [28]. These public smoking cessation clinics are attended by many smokers with low socio-economic status, people with mental problems, pregnant women, *etc.*, who have a high risk of relapse. E-cigarettes are not a miracle cure for smokers.

We have substantial evidence that the highest quit rates are achieved when offering intensive multi-session behavioural support combined with pharmacotherapy (varenicline or a combination of NRT (patch and *e.g.* spray, inhaler)) [29]. This is the “gold standard” treatment and high prolonged abstinence rates can be achieved. An RCT admitted patients with COPD to hospital for 2 weeks and offered gold standard smoking cessation treatment. More than 50% were abstinent in the intervention group after 1 year compared with 7% in the “usual care” group [30].

Based on this Cochrane review we can conclude that e-cigarettes might be more effective than NRT. The conclusions are applicable in a trial setting, but not in a population-based real-life setting. There is no evidence that we should recommend e-cigarettes instead of varenicline or bupropion. Smoking cessation counselling should still be recommended to all smokers, motivated as well as non-motivated.

Before we start recommending e-cigarettes to smokers, we must remember the Hippocratic Oath: “first do no harm”. The Cochrane review suggest that an additional four people for every 100 would quit smoking with nicotine e-cigarettes compared to NRT. We must question ourselves if the benefit of the four extra people who quit with e-cigarettes will out-weight the harms of long-term, maybe life-long, use of e-cigarettes in the many people who continue using them after smoking cessation. With current knowledge of the potential long-term health effects of e-cigarettes we wouldn't dare recommending them.

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