



## PRACTICE

## THERAPEUTICS

# Electronic cigarettes for smoking cessation

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### What you need to know

- Electronic cigarettes (e-cigarettes) were originally designed as a smoking cessation aid, and the limited evidence available suggests e-cigarettes containing nicotine may help people stop smoking
- Evidence suggests e-cigarettes are considerably safer than traditional cigarettes
- The technology used in e-cigarettes has evolved considerably over time, and newer devices are typically better at delivering nicotine, which might enhance effectiveness

### Cigarette and nicotine addiction

Most people who smoke cigarettes are addicted, and the main vehicle of that addiction is nicotine. When stopping smoking, people experience cravings for cigarettes, which drives return to smoking. These cravings for smoking are less intense when nicotine is substituted; thus replacing nicotine from sources other than cigarettes can facilitate achieving abstinence.

*A 42 year old electrician has tried to stop smoking several times, including with the aid of pharmacotherapy and behavioural support. He asks you about using electronic cigarettes (e-cigarettes). His work partner stopped smoking a year ago and is still using e-cigarettes now. He has heard that e-cigarettes are as damaging as the real things and worries that if he ends up addicted to e-cigarettes he'll not have gained anything.*

About 60% of current adult smokers in Great Britain have tried electronic cigarettes (e-cigarettes), and 18% are current e-cigarette users.<sup>1</sup> In England, over 40% of people who try to stop smoking do so with the aid of e-cigarettes.<sup>2</sup> About 52% of current e-cigarettes users are former smokers.<sup>1</sup> Some people who stop smoking with an e-cigarette are still using e-cigarettes a year later.<sup>1</sup> In this article we look at whether e-cigarettes help people who smoke to cut down and stop smoking, what are the health risks from e-cigarette use, and how these compare with smoking.

Transferring from cigarettes to other nicotine delivery devices, such as nicotine replacement therapy (NRT) or e-cigarettes, can transfer cigarette addiction to nicotine addiction. Around half of lifetime regular smokers will eventually die from smoking related causes,<sup>3</sup> whereas evidence on harms of addiction to NRT or e-cigarettes show it is much less hazardous. Moreover, while cigarette smoking is tenacious, only a minority of people who transfer to NRT (and do not return to smoking) are persistent users.<sup>4</sup> While there is less evidence on persistent use of e-cigarettes after quitting smoking, one French cohort study found that over half of people who quit smoking with the aid of e-cigarettes were no longer using e-cigarettes six months later.<sup>5</sup> Persistent users of NRT and e-cigarettes report doing so primarily to avoid a return to smoking.<sup>6,7</sup>

All nicotine delivery devices—cigarettes, NRT, and e-cigarettes—provide nicotine dose information. It is not possible to use this to compare the nicotine dose delivered across the types of devices, however, as the dose the user receives depends much more on how the device is used than the stated package dose.<sup>8</sup> Adding additional nicotine delivery devices, such as by using NRT or e-cigarettes while smoking, does not usually increase nicotine dose and tends to reduce tobacco dependence.<sup>9-11</sup>

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This is one of a series of occasional articles on therapeutics for common or serious conditions, covering new drugs and old drugs with important new indications or concerns. The series advisers are Robin Ferner, honorary professor of clinical pharmacology, University of Birmingham and Birmingham City Hospital, and Patricia McGettigan, clinical senior lecturer in clinical pharmacology, Queen Mary's University, London. To suggest a topic, please email us at [practice@bmj.com](mailto:practice@bmj.com).

**Search strategy**

We used the search terms and inclusion criteria from the Cochrane review of electronic cigarettes for smoking cessation.<sup>17</sup> Searches were updated on 23 March 2017 and included: Cochrane Tobacco Addiction Group Specialized Register; Cochrane Central Register of Controlled Trials (CENTRAL); MEDLINE; Embase; and PsycINFO. Search terms included e-cig\$ OR elect\$ cigar\$ OR electronic nicotine.

**What are electronic cigarettes?**

E-cigarettes heat a liquid into an aerosol for inhalation, which usually comprises propylene glycol and glycerol, with or without flavours (↴). Different models of e-cigarette are available, typically referred to as first, second, third, or fourth generation devices (↴). The “e-liquid” or “juice” is stored in disposable or refillable cartridges or a reservoir, depending on the type of device. E-liquid varies in its nicotine content, from liquid which contains no nicotine to liquid that contains doses >20 mg/mL. E-cigarette users are sometimes described as “vapers” and e-cigarette use as “vaping.”

E-cigarettes were originally designed as a smoking cessation aid. In those that contain nicotine, urges and withdrawal symptoms may be reduced by substituting the nicotine from tobacco smoke—as with more traditional forms of nicotine replacement therapy (such as nicotine patches or gum).<sup>15</sup> However, e-cigarettes may also facilitate smoking cessation by addressing the sensory and behavioural aspects of addiction to smoking cigarettes.<sup>16</sup>

**Licensing of e-cigarettes**

There are currently no countries where e-cigarettes have been licensed as medical products, though applications are in the pipeline.

Sales and marketing restrictions vary by country. In some countries, including Norway, Singapore and Brazil, e-cigarettes are banned, whereas in the US and EU, it is legal to sell e-cigarettes to adults. In the US, e-cigarettes now fall under the remit of the Food and Drug Administration (FDA) through the “deeming rule” which subjects them to the same regulations as other tobacco products. In the EU, e-cigarettes fall under the remit of the European Union Tobacco Products Directive, except where claims are made regarding therapeutic use or where nicotine content exceeds 20 mg/mL, in which case medical licensing is required.

**What the guidelines say**

A 2016 report from the Royal College of Physicians (UK) recommends that, in the interest of public health, it is important to promote the use of e-cigarettes, nicotine replacement therapy, and other non-tobacco nicotine products as widely as possible as a substitute for smoking.<sup>12</sup> However, medical guidelines have tended not to make definitive statements on the use of e-cigarettes because of limited evidence, with some regulators citing concerns regarding uptake in children. A 2016 statement on e-cigarettes from Public Health England and other UK public health organisations states that there is no circumstance in which it is better for a smoker to continue smoking, and that e-cigarette use among youth will continue to be closely monitored.<sup>13</sup> In 2017, Public Health England promoted the use of e-cigarettes as a smoking cessation aid.<sup>14</sup>

**How well do they work for quitting smoking?**

A 2016 Cochrane review of e-cigarettes (two randomised controlled trials, total number of participants 662) for smoking cessation found that e-cigarettes with nicotine might help people stop smoking for six to 12 months compared with placebo

e-cigarettes without nicotine (9% abstinence v 4%; relative risk 2.29 (95% confidence interval 1.05 to 4.96)).<sup>17</sup> However, certainty in this estimate was judged to be low due to imprecision (small number of trials and events) and indirectness (the two trials included in the review both used first generation devices which are no longer available because of poor nicotine delivery).<sup>18 19</sup> Compared with uncontrolled studies, in which participants provided with e-cigarettes showed quit rates ranging from 12.5% to over 50% for six months or longer, quit rates were relatively low in the randomised controlled trials, which could be due in part to the populations studied, relatively small sample sizes, devices tested, and the definitions of abstinence used.<sup>17</sup>

**How well do they work for cutting down?**

There is no definitive evidence that reducing cigarette consumption without quitting improves health.<sup>20</sup> For that reason, the 2016 Cochrane review of electronic cigarettes for smoking cessation did not address reduction.<sup>17</sup> However, people who want to reduce usually want to quit eventually, and there is evidence from a separate Cochrane review that, in people unmotivated to quit, providing NRT to help people initially reduce their cigarette consumption can lead to increased quit rates in the longer term.<sup>21</sup> It therefore follows that nicotine-containing e-cigarettes may also be helpful in promoting reduction and abstinence, but the 2016 Cochrane review of tobacco harm reduction interventions included only one small study of e-cigarettes, meaning there was insufficient direct evidence to conclude this.<sup>19 21</sup>

**What are the harms?**

Studies conducted in people using e-cigarettes to quit smoking have not detected serious adverse effects, and the devices seem well tolerated by people who smoke. However, as e-cigarettes have been used for only a few years, there is scant epidemiological data on the safety of e-cigarettes when used as a long term or permanent replacement for smoking. Most studies which have reported on safety of e-cigarettes were small, uncontrolled, and followed participants for six months or less, and therefore the Cochrane review of e-cigarettes judged the quality of evidence on adverse events from e-cigarettes as low.<sup>17</sup> As almost all regular use of e-cigarettes occurs in former or current smokers, interpreting future epidemiological data will be difficult, though longer term studies are under way (see “Ongoing studies” in Cochrane review<sup>17</sup>). Based on comparisons of the composition of carcinogens and toxicants in tobacco smoke and e-vapour, a 2016 Royal College of Physicians report estimated that the harm arising from long term vapour inhalation from e-cigarettes is unlikely to exceed 5% of the harm from smoking tobacco.<sup>12</sup> Although many have criticised this figure, there is consensus among public health experts that smoking is more dangerous than vaping.

Many studies—mostly small and uncontrolled—have investigated aspects related to the safety of e-cigarettes. Findings on individual outcome groups and key biomarkers are summarised in Boxed Text on page 3 box 1 and ↴, drawing on the 2016 Cochrane review of e-cigarettes<sup>17</sup> but updated to include relevant studies published since.

Box 1 Summary of adverse events reported in longitudinal studies of e-cigarettes used for a week or longer

**2016 Cochrane review<sup>17</sup> (14 studies (4 RCTs, 10 observational), total n=1722)**

- No serious adverse events reported that were considered plausibly related to e-cigarette use, either in exclusive users (switched entirely to e-cigarettes) or dual users (who used e-cigarettes but continued to smoke). Longest follow-up was 2 years
- No RCTs found statistically significant differences in adverse events by treatment arm. Studies included exclusive e-cigarette users and dual users, with longest follow-up of 1 year
- The most frequently reported adverse events across studies were mouth and throat irritation, cough, nausea, and headache, usually dissipating over time

**Trials of e-cigarettes with nicotine versus e-cigarettes without nicotine<sup>18-23</sup> (3 RCTs, total n=421)**

- Pooled results from the trials found a similar percentage of adverse events between groups (risk ratio 1.18 (95% CI 0.87 to 1.56))

**Trial of e-cigarettes with nicotine versus nicotine patch (six month follow-up)<sup>18</sup> (1 RCT, n=456)**

- 44.4% in e-cigarettes arm reported any adverse event, compared with 44.7% in patch arm (risk ratio 0.99 (0.81 to 1.22))

RCT = randomised controlled trial.

## Safety in people with pre-existing conditions

Results from individual studies in people with chronic obstructive pulmonary disease, asthma, and hypertension have generally shown improvements in symptoms and have not detected serious adverse effects. We found no studies providing evidence regarding the safety of e-cigarette use during pregnancy. Findings in these populations from retrospective chart reviews are summarised in [↓](#).

## What happens in people who cut down tobacco smoking but don't stop?

Most studies of e-cigarettes compare people using them exclusively with people exclusively using combustible forms of tobacco. However, dual use is common in the general population.<sup>1</sup> There are no long term data on the safety of dual use, but data from one short term study detected reductions in toxicants in people who switched from using only combustible tobacco to using combustible tobacco and e-cigarettes.<sup>10</sup> None of the included studies in the Cochrane review found an increase in adverse events or undesirable changes in biomarkers in people who began using e-cigarettes in addition to combustible tobacco.<sup>17</sup> However, there is no definitive evidence that reducing cigarette consumption without quitting improves health.

## How do they compare with other nicotine replacement therapies?

Only one randomised controlled trial with long term follow-up is available comparing e-cigarettes with nicotine replacement therapy. In the ASPIRE trial, participants were randomised to e-cigarettes with nicotine, e-cigarettes without nicotine (placebo), or nicotine patch for 13 weeks. Neither adverse events

nor quit rates were significantly different between those assigned to e-cigarettes with nicotine and those assigned to patch, though confidence intervals do not rule out an important difference for six-month cessation (risk ratio 1.26 (95% CI 0.68 to 2.34), 584 participants).<sup>18</sup>

Multiple trials are ongoing comparing e-cigarettes with traditional forms of nicotine replacement therapy (NRT).<sup>17</sup> At present there are only two completed randomised controlled trials of e-cigarettes for smoking cessation with follow-up at six months or longer, whereas there are over 100 definitively establishing the efficacy and safety of nicotine replacement therapy for smoking cessation.<sup>15 17</sup> The Royal College of Physicians has stated that, as e-cigarettes are not currently made to medicines standards, they are “probably more hazardous than NRT.”<sup>12</sup>

## How cost effective are they?

Though other forms of NRT are often paid for by healthcare systems, e-cigarettes are not as they are not medically licensed. There are no evaluations of cost effectiveness.

### Tips for patients

- Smoking is uniquely deadly, and the evidence we have so far suggests electronic cigarettes (e-cigarettes) with nicotine may help you quit
- There is strong evidence that behavioural support and commonly used medications to help stop smoking—including nicotine replacement therapy, varenicline, and bupropion—are useful and safe to use. There is less evidence available on the effectiveness and safety of e-cigarettes as they are relatively new products
- It is probably best to try a second generation e-cigarette (often referred to as vape pens). First generation devices (cig-a-likes, which look like cigarettes) deliver less nicotine and may be less satisfying and not work as well. Third and fourth generation devices may be more complicated to use for people new to e-cigarettes
- It takes time to learn to use an e-cigarette to replace smoking, so persevere by changing the dose of nicotine, type of device, and the flavours. Ask a friend or ask for help in a vape shop. Once you are finding your electronic cigarettes satisfying, plan a day on which you will quit smoking regular cigarettes as soon as you can
- Though we can't say e-cigarettes are 100% safe, experts overwhelmingly agree that they are considerably less harmful than traditional cigarettes. Some experts estimate that e-cigarettes are 95% safer than traditional cigarettes
- The harm from smoking comes from burning the tobacco, not from the nicotine. As with other forms of nicotine replacement therapy, try not to worry about continued use of nicotine—the most important thing is to stop smoking

### Education into practice

- What specific learning points from this article would you share with colleagues who work in different disciplines?
- Now you have read this article, how will you discuss the available evidence about the benefits and harms of e-cigarettes with patients who have tried other ways to quit?

How patients were involved in the creation of this article

We held discussions with three members of the UK Centre for Tobacco and Alcohol Studies smokers' panel before drafting the article; these discussions informed what was included in the sections on safety and tips for patients. Panel members also commented on the full article, resulting in revisions to the tips for patients.

**Competing interests** We have read and understood the BMJ policy on declaration of interests and declare the following interests: There was no specific funding for this article. JHB and RB receive support from the National Institute of Health Research. PA is funded by the UK Centre for Tobacco and Alcohol Studies and is supported by the NIHR Biomedical Research Centre, Oxford and the NIHR CLAHRC, Oxford. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health. JHB, PA, and RB have no other competing interests to declare.

**Contributors** JHB, RB and PA all contributed to the conception and design of the work; the acquisition, analysis, and interpretation of the data; the drafting and revision of the manuscript critically for important intellectual content; and final approval of the version to be published. JHB is guarantor.

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## Tables

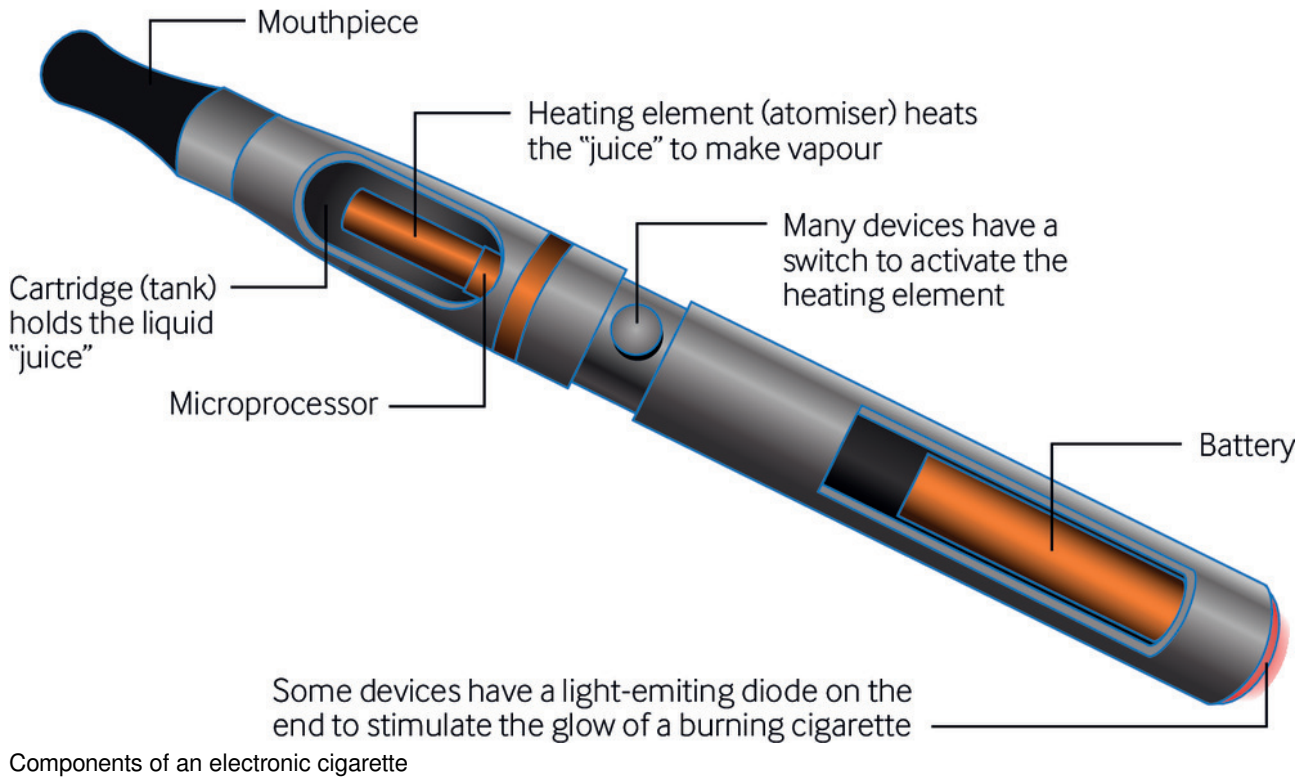
**Table 1 | Summary of changes in tobacco toxicant biomarkers reported in longitudinal studies of smokers who switched partially or fully to e-cigarettes for at least a week\***

| Comparison†                                                            | Summary of results                                                                                                                                                                                                                                                                                  | Study duration      | Sample size                                |
|------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------|--------------------------------------------|
| <b>Exhaled carbon monoxide (CO)</b>                                    |                                                                                                                                                                                                                                                                                                     |                     |                                            |
| e-cigarettes v continuing smoking                                      | Statistically significant declines in e-cigarette users; no significant changes in continuing smokers who did not use e-cigarettes <sup>17,24</sup>                                                                                                                                                 | 4 weeks to 8 months | 3 studies (2 RCTs, 1 observational), n=490 |
| Nicotine e-cigarettes v non-nicotine e-cigarettes                      | No differences between groups <sup>22,23</sup>                                                                                                                                                                                                                                                      | 1 to 3 weeks        | 2 RCTs, n=123                              |
| Before-after provision of and instruction to use e-cigarettes          | Statistically significant declines from baseline to follow-up in both exclusive e-cigarette users and dual users <sup>17,25,27</sup>                                                                                                                                                                | 1 week to 2 years   | 8 studies (3 RCTs, 5 observational), n=344 |
| <b>Known tobacco-related carcinogens</b>                               |                                                                                                                                                                                                                                                                                                     |                     |                                            |
| e-cigarettes v continuing smoking                                      | Declines in three carcinogens in both groups, but changes were statistically significant in e-cigarette users only; statistically significant group differences observed <sup>24</sup>                                                                                                              | 12 weeks            | 1 RCT, n=408                               |
| Before-after study of provision of and instruction to use e-cigarettes | Statistically significant reductions in at least some of the measured toxicants in both exclusive e-cigarette users and dual users. No studies found increases in any of the toxicants measured <sup>17,28</sup>                                                                                    | 10 days to 4 weeks  | 3 studies (1 RCT, 2 observational), n=97   |
| <b>Blood pressure</b>                                                  |                                                                                                                                                                                                                                                                                                     |                     |                                            |
| e-cigarettes v continuing smoking                                      | General population: no clinically or statistically significant group differences <sup>24</sup><br>People with hypertension: systolic and diastolic blood pressure statistically significantly lower at 12 months in e-cigarette users (exclusive and dual) than in continuing smokers <sup>29</sup> | 12 weeks to 2 years | 2 studies (1 RCT, 1 observational), n=497  |
| Nicotine e-cigarettes v non-nicotine e-cigarettes                      | No significant (clinical or statistical) changes among or between groups <sup>30</sup>                                                                                                                                                                                                              | 1 year              | 1 RCT, n=300                               |
| <b>Heart rate</b>                                                      |                                                                                                                                                                                                                                                                                                     |                     |                                            |
| e-cigarettes v continuing smoking                                      | No clinically significant changes in people who switched from smoking alone to partial or exclusive use of e-cigarettes <sup>24,30</sup>                                                                                                                                                            | 12 weeks to 1 year  | 2 RCTs, n=708                              |
| Nicotine e-cigarettes v non-nicotine e-cigarettes                      | No significant (clinical or statistical) changes among or between groups <sup>30</sup>                                                                                                                                                                                                              | 1 year              | 1 RCT, n=300                               |
| <b>Lung function (including FEV<sub>1</sub>, FVC)</b>                  |                                                                                                                                                                                                                                                                                                     |                     |                                            |
| e-cigarettes v continuing smokers                                      | No clinically significant changes (one study in healthy volunteers, one in people with COPD) <sup>24,31</sup>                                                                                                                                                                                       | 12 weeks to 2 years | 2 studies (1 RCT, 1 observational), n=456  |
| Before-after study of provision of and instruction to use e-cigarettes | Statistically significant improvements over a 2 year period (study in people with asthma) <sup>32</sup>                                                                                                                                                                                             | 2 years             | 1 observational, n=18                      |

Table 2| Summary of findings from studies of e-cigarette use in people with pre-existing conditions

| Condition                                    | Study details                                                                                                                                                        | Findings                                                                                                                                                                                                                                                                            |
|----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Asthma                                       | Uncontrolled study of people who smoked and switched to e-cigarettes using 2 years of data from medical records (n=18) <sup>32</sup>                                 | No evidence of harm<br>Statistically significant improvements in asthma control questionnaire (ACQ) scores and lung function parameters over study period                                                                                                                           |
| Hypertension                                 | Two year study of blood pressure readings from medical records comparing people with hypertension who continued smoking with those who switched (n=89) <sup>29</sup> | E-cigarette use well tolerated<br>No severe adverse reactions or acute decompensation in blood pressure in e-cigarette users<br>Statistically significantly lower systolic and diastolic blood pressure in e-cigarette users than in matched tobacco smokers at 12 months (P<0.001) |
| Chronic obstructive pulmonary disease (COPD) | Two year study of data from medical records comparing people with COPD who continued smoking with those who switched (n=48) <sup>31</sup>                            | Statistically significant reduction in COPD exacerbations in e-cigarette users, from 2.3 (SD 1.0) at baseline to 1.8 (SD 1.0, P=0.002) at 1 year and 1.4 (SD 0.9, P<0.001) at 2 years. No changes in matched controls                                                               |

## Figures





Different generations of electronic cigarettes