

# Electronic cigarettes: a brief update

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More people are using electronic cigarettes (e-cigarettes) and fewer people are smoking conventional tobacco cigarettes. A wide variety of e-cigarettes are available and there is emerging evidence that they may help with smoking cessation. This evidence-based clinical review summarises the latest evidence regarding use of e-cigarettes as smoking cessation aids. The ongoing debate surrounding the safety and regulation of e-cigarettes is also discussed.

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## Introduction

Smoking remains the leading preventable cause of illness and premature death. In 2015, it caused more than one-tenth of worldwide deaths, killing around 6 million people, and was associated with a global loss of nearly 150 million disability-adjusted life-years.<sup>1</sup> Readers of *JRCPE* will be cognisant of the changing epidemiology of smoking: a fall in conventional cigarette use, coupled with a steady increase in ‘vaping.’ Indeed, it is estimated that there are currently around 2.9 million adult electronic cigarette (e-cigarette) users in the UK.<sup>2</sup> A total of 60% of adult conventional cigarette smokers have tried e-cigarettes and 18% use both.<sup>2</sup> Smokers are asking healthcare professionals whether e-cigarettes are safe and effective for smoking cessation: is vaping the alternative that could curb smoking-related harms? In this review, we summarise the latest evidence, to inform such discussions.

## Search strategy

We based our review on recently published guidelines by Royal College of Physicians (2016)<sup>3</sup> and Public Health England (2018),<sup>4</sup> in addition to searching PubMed using the terms “vaping”, “electronic cigarettes” and “smoking cessation”.

## Epidemiology

### Tobacco cigarettes

The Royal College of Physicians highlighted recent smoking trends in the UK, in a 2016 report.<sup>3</sup> They estimated that there were approximately 8.7 million adult smokers, but the

prevalence was falling – in 1972 51% of men and 41% of women smoked, compared to 2014 figures of 21% and 16%, respectively.<sup>3</sup> Smoking remains most common in young adult men (aged 25–34 years), individuals from disadvantaged socioeconomic backgrounds, the unemployed and those with long-standing mental health conditions.<sup>3</sup> Smoking rates in children are falling markedly, from 9% to 3% over the past 10 years in the 11–15 years age group.<sup>3</sup> This is pertinent as most UK smokers start during their teenage or early adult years.<sup>4</sup>

### E-cigarettes

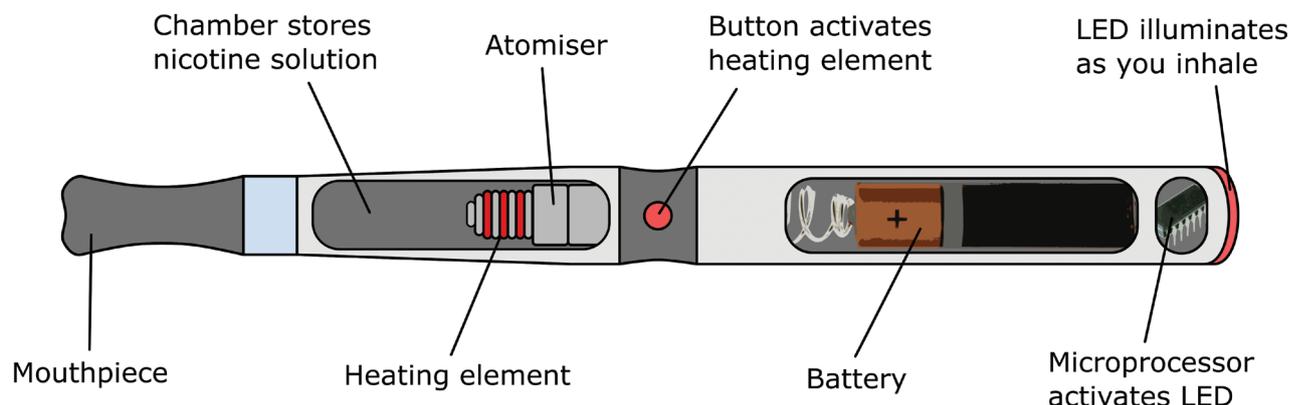
In 2017, 2.9 million adults (about 6% of the population) used e-cigarettes in the UK.<sup>2</sup> The prevalence of e-cigarette use in current smokers has plateaued, while that in ex-smokers continues to increase. Only 3% of all e-cigarette users are never smokers.<sup>2</sup> Over time the proportion of ‘dual users’ (current e-cigarette users who also smoke tobacco) has fallen and the proportion who are ex-smokers has risen. Indeed, by 2017 there were more ex-smokers (1.5 million, 52% of all vapers) who use e-cigarettes than current smokers (1.3 million, 45% of all vapers). An independent review by Public Health England concluded that e-cigarettes are not undermining the long-term decline in cigarette smoking in the UK among young people, despite some vaping experimentation among never smokers.<sup>4</sup>

## What are e-cigarettes?

E-cigarettes deliver nicotine to the lungs. Conventional tobacco-containing cigarettes also do this, but importantly also deliver aerosolised particles containing carcinogens, toxins and oxidising agents, deep into the lungs. In addition, tobacco cigarette smoke is released by the

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**Figure 1** Schematic of electronic cigarette elements. The stylised diagram is a schematic representation of the various different elements of an electronic cigarette



burning cigarette tip, thus releasing toxins into the atmosphere ('second-hand smoking').

### How do e-cigarettes work?

They contain a battery, and to activate an in-built heating element the user either pushes a button or inhales through the mouthpiece. The heating element then vaporises 'e-liquid', stored in a reservoir or refillable cartridges (Figure 1). The vapour is inhaled into the lungs to deliver nicotine and only released into the surrounding atmosphere when the user exhales. The e-liquid contains varying amounts of nicotine, propylene glycol or vegetable glycerol, with or without flavourings. Thousands of flavours are available, and fruit, tobacco and menthol or mint remain the most popular.<sup>2</sup>

### Types of e-cigarettes

There are many varieties of e-cigarettes and the market is expanding. The design of these e-cigarettes has evolved substantially over time as shown through their several 'generations' (Figure 2).<sup>5</sup>

- First-generation devices were designed to resemble conventional tobacco cigarettes and were either disposable or rechargeable. These early devices were inefficient at nicotine delivery as the particle size could not penetrate deep into the lungs.
- 'Tank' models (vape pens) are rechargeable e-cigarettes with a tank or reservoir for the e-liquid. They can be open tank (e-liquid refilled manually by user) or closed tank (ready-made refills). Open tanks are more popular.
- 'Mods' (or advanced personal vaporisers) are customisable devices that allow users to adjust the voltage. Notably, running at higher temperatures increases nicotine delivery and amount of formaldehyde and other toxins produced in the aerosol.<sup>6</sup>
- Newer generation devices include JUULs, which are flat, rectangular portable e-cigarette devices. JUUL devices were designed to look like a computer flash drive. They have a 'JUULpod' (prefilled e-liquid cartridge, around 59 mg/ml nicotine per pod) and a device with battery and

temperature regulation.<sup>7</sup> JUUL devices were also the first to incorporate nicotine salts into e-cigarettes, which are believed to better mimic the nicotine 'hit' of conventional cigarettes.<sup>8</sup>

Although e-cigarettes were initially manufactured predominantly by tobacco companies, JUUL devices, produced by start-ups, have transformed the e-cigarette market by taking majority of the retail share.<sup>7</sup> We will undoubtedly see major changes in this market over the next few years, akin to those seen in the tech industry.

### Nicotine pharmacology

Nicotine is a naturally occurring alkaloid found in the leaves of the tobacco plant, where it acts as an insecticide. There is a widespread misperception that nicotine is a harmful substance, but nicotine inhalation at commonly used doses does not result in clinically significant harm.<sup>3,9</sup> However, nicotine is highly addictive, and it has been suggested that people 'smoke for the nicotine but die from the tar'.<sup>10</sup>

Crucially, the addictiveness of nicotine depends on how it is administered. Inhaling tobacco is a faster nicotine delivery route to the brain than intravenous administration. As tobacco smoke is inhaled, it diffuses through the alveoli to reach the brain within 10–20 s. Here, nicotine exerts its pharmacological effects by binding to the nicotinic acetylcholine receptors and triggering release of dopamine and other neurotransmitters.<sup>3,11</sup> This has various consequences:

- Reward: stimulation of dopaminergic neurons in the ventral tegmental area produces rewarding effects.<sup>12</sup> At relatively low doses, nicotine also acts as a stimulant to increase heart rate and even improve attention and memory.
- Reinforcement: along with activation of the reward pathway, specific sensory and environmental cues (such as taste and smell of tobacco) reinforce smoking behaviour through conditioning.<sup>13</sup>

**Figure 2** Different generations of electronic cigarettes

- Tolerance: owing to changes in nicotinic receptor pharmacology, tolerance can develop quickly and lead to nicotine withdrawal effects, including irritability and anxiety.<sup>11</sup> This drives people to get further nicotine ‘hits’ via smoking or vaping.

Nicotine addiction is a chronic, relapsing condition, and involves reinforcements through environmental cues and the avoidance of withdrawal symptoms.<sup>12</sup> The value of e-cigarettes, as a nicotine delivery system in ex-smokers, to prevent relapse back to tobacco smoking, is an important area that requires further study.

## E-cigarettes for smoking cessation

In 2018, the Royal College of Physicians published *Hiding in Plain Sight: Treating Tobacco Dependency in the NHS*, a report that calls for a change in the way UK smoking-cessation services are delivered.<sup>14</sup> The report recommends moving away from an ‘opt-in’ model (where healthcare professionals only offer smoking cessation aids when smokers are ready to quit) to an ‘opt-out’ model (where smoking cessation aids are offered regardless of the smoker’s motivation). Stopping smoking before age 30 years, regains 10 years of life otherwise lost, and stopping at age 40, 50 and 60 years, can regain 9, 6 and 3 years, respectively.<sup>15</sup> There are several different strategies available to aid smoking cessation, including behavioural support, nicotine replacement and pharmacological treatments.<sup>16</sup> E-cigarettes were originally designed as smoking-cessation aids,<sup>17</sup> and have even been incorporated into national smoking-cessation guidelines.<sup>18</sup>

In 2017, smoking quit rates were at their highest and parity across different socioeconomic groups was observed. It is plausible that e-cigarette use has contributed to this. Beard and colleagues performed a time-series analysis and

found that changes in the prevalence of vaping in England were positively associated with quitting success.<sup>19</sup> One of the most commonly cited reasons for vaping is to quit smoking: approximately half a million people are vaping for this purpose.<sup>2,20</sup> Self-reported quit rates were higher when people used e-cigarettes. One cross-sectional English study (n = 5,863) by Brown and colleagues found that smokers using e-cigarettes were significantly more likely to remain 1-year abstinent than those quitting unaided or using over-the-counter cessation aids.<sup>21</sup>

As the number of vapers surpasses the number of people smoking conventional cigarettes, some public health experts are claiming that there is potential for significant ‘harm reduction’ and public health benefit with vaping.<sup>22</sup> However, other experts disagree and feel that there is more public harm if nonsmokers start vaping and dual users continue to smoke and vape, as this not only undermines complete abstinence, but also re-normalises smoking in a society that should ideally be smoke free.<sup>23,24</sup> It is important to appraise the limited evidence available before judgement is made.

## Evidence for smoking cessation: randomised trials

A 2016 Cochrane review of smoking cessation concluded that nicotine e-cigarettes might help people stop smoking for 6–12 months compared to placebo non-nicotine e-cigarettes.<sup>25</sup> Similar conclusions were drawn by two other meta-analyses.<sup>26,27</sup> However, only two randomised controlled trials have been the sources for these conclusions:

- Bullen et al. compared 3 months of nicotine e-cigarettes, placebo non-nicotine e-cigarettes and redeemable nicotine patch vouchers (n = 657) for verified sustained abstinence rates.<sup>28</sup> At 6 months follow up, there was no significant difference between nicotine e-cigarettes and patches (p = 0.46) and between nicotine and placebo e-cigarettes (p = 0.44). Notably, the trial used first-generation devices that are no longer available owing to poor nicotine delivery. Furthermore, participants were given e-cigarettes but only handed vouchers for patches and this likely overstated the efficacy of vaping.
- The ECLAT study was a prospective randomised controlled trial that compared 3 months of nicotine e-cigarettes (7.2 mg for 12 weeks and a second group with 7.2 mg for 6 weeks followed by 5.4 mg for 6 weeks) and non-nicotine e-cigarettes in smokers not intending to quit (n = 300).<sup>29</sup> The study found no significant differences between these groups at 12 months follow up (p = 0.24) but found that users reduced their cigarette use. The lack of an appropriate control group (smokers not using e-cigarettes) limits the conclusions regarding the benefits of smoking cessation.

In a very recent pragmatic trial of smoking cessation (n = 6,131), Halpern et al. found that financial incentives with free smoking-cessation aids resulted in a higher rate of sustained quitting than free cessation aids alone.<sup>30</sup> There was no statistically significant difference in 6-month abstinence rates between free e-cigarettes and usual care

(information provision,  $p = 0.20$ ) and free cessation aids ( $p = 0.43$ ).<sup>30</sup> Of note, smoking cigarettes in the UK currently costs around twice as much as using e-cigarettes.<sup>31</sup> These financial factors will bear significance to e-cigarettes' utility in smoking cessation.

#### Evidence for smoking cessation: observational studies

Uncontrolled studies show higher abstinence rates than randomised trials. These lower quit rates have been attributed to various factors including the populations studied, the small sample sizes and the devices used. Most observational studies compare cigarette use among smokers who did, or did not, use e-cigarettes. An analysis of eight cohort studies found no benefit with e-cigarettes.<sup>26</sup> Another meta-analysis appraised the available data in a 'real world' approach by including all available studies that had quantitative estimates between e-cigarettes and smoking cessation.<sup>32</sup> The authors concluded that e-cigarette use significantly lowered quitting rates.<sup>32</sup> An updated analysis led to the same conclusion: smokers who vape are less likely to quit.<sup>5</sup> However, vaping pattern could be a potential confounding factor. Smokers who vape daily have higher quit rates than those who only occasionally vape.<sup>5</sup>

#### Harms associated with e-cigarettes

Smoking conventional cigarettes is associated with premature death through lung cancer, cardiovascular disease, chronic obstructive pulmonary disease and other diseases.<sup>1</sup> Although most authors reasonably highlight that experience and studies are limited, there appears to be a growing acceptance that vaping is safer than tobacco cigarettes. Public Health England has stated that e-cigarettes are '95% safer' than conventional cigarettes, given the reduction in carcinogen load.<sup>3,4</sup> NHS Scotland have echoed this statement and are supported by many organisations including the Royal College of Physicians of Edinburgh and the Chief Medical Officer for Scotland.<sup>33</sup> Nonetheless it is important that we are not complacent about possible harm associated with e-cigarettes, and below we discuss some emerging data on potential risks.

#### Carcinogenic potential

Smokers who switch to solely vaping would be expected to reduce their cancer risk, as they limit exposure to >70 known carcinogens in conventional tobacco smoke.<sup>5</sup> The cancer potency of e-cigarettes has been estimated to be <0.5% than that of smoking tobacco.<sup>4</sup> The National Academies of Sciences, Engineering and Medicine from the USA recently found no available evidence linking e-cigarette use to intermediate cancer endpoints in humans.<sup>34</sup>

#### Cardiovascular and noncancer lung disease

Cardiovascular disease kills more smokers than cancer.<sup>5</sup> There is no safe level of smoking for cardiovascular disease. Smoking even one cigarette per day equates to a third of the stroke risk and up to half the cardiac risk compared to smoking 20 per day.<sup>35</sup> It is known that ultrafine particles, delivered to the blood stream via smoking, can trigger inflammatory processes harmful to the cardiovascular system.<sup>36</sup> Vaping

also delivers these ultrafine particles. Indeed, e-cigarette users experience oxidative stress that could influence primary haemostasis.<sup>5</sup> These pathophysiological changes may underlie the preliminary findings between e-cigarette use and heart disease. A cross-sectional analysis of US health surveys ( $n = 69,725$ ) found that daily e-cigarette users had higher chance of suffering a myocardial infarction ( $p = 0.004$ ) after adjusting for potential confounding variables including smoking.<sup>37</sup> This was not true of occasional or former e-cigarette users.<sup>37</sup> Scott et al. have recently demonstrated that e-cigarette vapour in vitro can induce an inflammatory phenotype in alveolar macrophages and can potentially impair bacterial clearance by inhibiting phagocytosis.<sup>38</sup>

#### Gateway to tobacco and other drugs

The 'gateway hypothesis' suggests that young people become sequentially involved in drugs in stages. There has been some concern about the potential of e-cigarettes to act as a gateway into young people smoking. We need to be cautious about the effects of vaping on the young brain and the potential for addicting a new generation. Molecular studies suggest that nicotine exerts a priming effect through global acetylation changes in the striatum, and various epidemiological studies have demonstrated that nicotine can act as a gateway to the use of cocaine and marijuana.<sup>13</sup>

Among British youth, the number of never smokers who have tried an e-cigarette increased from 18% in 2014 to 29% in 2016.<sup>2</sup> A recent UK-based questionnaire study involving students aged 11–16 years found that knowledge of e-cigarettes was limited, and most adolescents used e-cigarettes for experimentation.<sup>39</sup> However, Public Health England argues that despite experimentation among never smokers, e-cigarettes are not contributing to any rise in youth smoking.<sup>4</sup> It is important to distinguish the large number of British youth who have only vaped once or twice while experimenting with the small minority that regularly use e-cigarettes. A recent British survey ( $n = 2,291$ ) found that only 2% of youths vape at least once a week.<sup>40</sup> Worryingly, with the rise of start-ups like JUUL (currently banned in Europe due to nicotine content), American studies are finding 'substantial evidence' that e-cigarette use increases the risk of young people subsequently smoking and 'moderate evidence' that it increases overall subsequent tobacco use.<sup>34</sup> These findings are corroborated by meta-analyses that are suggesting that e-cigarette use in people aged 14–30 years is associated with a greater risk of subsequent smoking.<sup>41</sup>

#### Poisonings, fires and explosion

Harm can also be caused by exposure to e-liquids (poisoning) and injuries from fires and exploding e-cigarettes or their batteries. Incidents of these natures often gain significant media attention. There have only been minimal recorded cases of e-liquid poisonings in the UK. This has mostly been attributed to accidental ingestion.<sup>4</sup> The toxic effects are generally short and of minimal severity. Fires from e-cigarettes are believed to occur through malfunctioning batteries. There have been no recorded fatalities in the UK, but exploding e-cigarettes can cause severe burns and injuries.<sup>4</sup>

## Legislation and regulation

With the emerging evidence of e-cigarettes, there are specific challenges on how to best regulate these products. Currently, there is significant worldwide variation in the regulation of e-cigarettes and their legal status is currently pending in many countries. A report by the World Health Organization Convention on Tobacco Control has highlighted the importance of regulatory measures to ensure that vaping does not worsen the tobacco epidemic.<sup>42</sup>

In the UK, there is an ongoing debate about the regulation of e-cigarettes. Members of Parliament have recently written a report to the Government asking for greater advertising freedom, relaxation of tax duties, an annual review on the health effects of e-cigarettes, a debate on vaping in public spaces, licensing of e-cigarettes as medical devices and a consideration given to the limits on refill strengths and tank sizes.<sup>43</sup>

Currently, the use, sale and advertising of e-cigarettes are legal in the UK. It is, however, illegal to sell e-cigarettes to minors. As of May 2017, the European Union's Tobacco Products Directive regulations state that e-cigarette manufacturers need to restrict the maximum volume of e-liquid refill container

(10 ml) and restrict the nicotine concentration (<20 mg/ml) – precluding the sale of JUUL devices in Europe.<sup>44</sup> All e-cigarettes and liquids sold within the UK must also be registered by their respective manufacturers before they can be legally sold. E-cigarettes are also not covered by the smoking legislation, which bans the use of cigarettes in all enclosed public and work places; however, some organisations have prohibited the use of e-cigarettes in public spaces.<sup>43</sup>

## Summary

- Fewer people are smoking conventional tobacco cigarettes and more people are using (vaping) e-cigarettes.
- A wide variety of e-cigarettes are available, and this is likely to increase.
- E-cigarettes are being used as smoking cessation aids, although the evidence of any benefit in continued smoking abstinence is limited, with few high-quality trials.
- Debate continues regarding safety of e-cigarettes, but NHS Scotland and England have concluded that vaping e-cigarettes are less harmful than smoking tobacco. ①

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