



Public Health
England

Electronic cigarettes

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England

Authors: Professor John Britton and Dr Ilze Bogdanovica

UK Centre for Tobacco and Alcohol Studies

Division of Epidemiology and Public Health, University of Nottingham



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Public Health England
133-155 Waterloo Road
Wellington House
London SE1 8UG
Tel: 020 7654 8000
www.gov.uk/phe
Twitter: @PHE_uk
Facebook: www.facebook.com/PublicHealthEngland

Authors: Professor John Britton and Dr Ilze Bogdanovica
UK Centre for Tobacco and Alcohol Studies
Division of Epidemiology and Public Health, University of Nottingham
Clinical Sciences Building
City Hospital
Hucknall Road
Nottingham
NG5 1PB

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1. The public health impact of tobacco smoking in the UK

1.1 Background: Mortality and morbidity from smoking in adults, children, and the fetus

Smoking is the largest avoidable cause of death and serious disability in the UK and most other developed countries, and a global health threat. There are about one billion smokers worldwide, of whom about half will die prematurely as a direct consequence of their smoking, unless they quit.^[1] In the UK around one in five adults, or about ten million people, are current smokers,^[2, 3] five million of whom are expected to die prematurely from smoking, losing a total of around 100 million years of life.^[4] Smoking currently accounts for around 100,000, or about one in six, deaths each year in the UK.^[5]

Smoking causes around 85% of the approximately 40,000 cases of (and deaths from) lung cancer in the UK each year,^[6] and contributes to the development of many other cancers, including oral cavity cancer, oesophageal and gastric cancer, kidney and bladder cancers, and pancreatic cancer.^[7] Smoking also accounts for about 85% of the 23,000 deaths from chronic obstructive pulmonary disease (COPD) each year in the UK, and about 25,000 of the more than 200,000 deaths from cardiovascular disease.^[5] Smoking also increases the risk of pneumonia, asthma exacerbation,^[7] and a wide range of other adverse health effects.^[8]

Exposure to second-hand smoke (also referred to as passive smoking) also causes significant harm. Among adults, passive smoking causes thousands of deaths from lung cancer, cardiovascular disease and COPD.^[9] Passive exposure of children increases the risk of sudden infant death syndrome, lower respiratory infections, asthma and wheezing illness, meningitis and middle ear disease.^[10] Smoking during pregnancy harms the fetus, increasing the risk of premature birth, low birth weight, fetal anomalies, and fetal mortality.^[10]

1.2 Contribution of smoking to social inequalities in health and poverty

Smoking is strongly associated with socioeconomic disadvantage, and in most high income countries the prevalence of smoking is considerably higher among more deprived people than in those from affluent backgrounds.^[11] In the UK, the unemployed are twice as likely to be smokers compared to employed people,^[12] and smoking is highly prevalent among the homeless,^[13] those in prison,^[14] and other marginalised or otherwise highly disadvantaged groups. Smoking is also more than twice as prevalent among people with mental disorders than in the general population, and has changed little over the past 20 years, in contrast to the progressive decline in smoking

prevalence in the general population.^[15] Smokers in disadvantaged groups have also typically started to smoke at a younger age, smoke more cigarettes per day, and take in more nicotine from each cigarette.^[16] Smoking thus strongly exacerbates health inequalities.^[17]

2. Electronic cigarettes

2.1 Short history and description of products on the market

Electronic cigarettes (also known as e-cigarettes or electronic nicotine delivery systems (ENDS)) were invented in China in 2003^[18] and designed to provide inhaled doses of vaporized nicotine.^[19] Electronic cigarettes were first introduced to Europe in about 2005 and become increasingly popular since. The products have evolved and improved considerably, such that while most early models resembled cigarettes in shape and size^[19] (sometimes referred to a ‘cigalikes’, figure 1), many later ENDS models are larger, at about the size of a conventional fountain pen, and are known (among other terms) as ‘personal vapourisers’, or PVs (figure 2).

Electronic cigarettes typically comprise a re-chargeable lithium ion battery, and a battery powered atomiser which produces vapour by heating a solution of nicotine, usually in propylene glycol or glycerine, held in a (often refillable) cartridge in the device (figure 1). Drawing air through the e-cigarette triggers the heater to create vapour which contains nicotine and is inhaled by a smoker the same way as smoke from conventional cigarettes. Producing nicotine vapour from a solution rather than by burning tobacco means that electronic cigarette vapour is free from almost all of the many toxic chemicals that accompany nicotine in cigarette smoke. Not all electronic cigarettes include nicotine; some simply produce vapour for inhalation, but these are not popular among users.^[20]

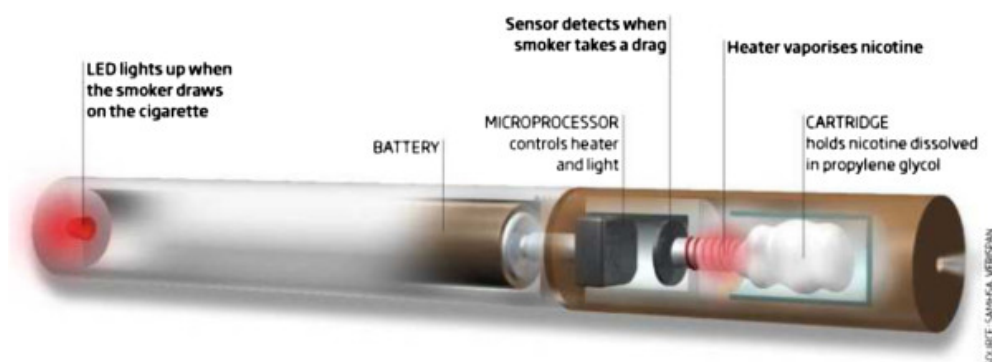


Figure 1: An electronic cigarette (reproduced from Polosa et al. A fresh look at tobacco harm reduction: the case of electronic cigarettes^[19])



Figure 2: an example of a personal vapouriser (from Wikipedia, <http://en.wikipedia.org/wiki/File:E-cigarette.jpg>)

2.2 Nicotine content, delivery and pharmacokinetics

Evidence on the content and emission of electronic cigarettes is limited. As nicotine is the addictive substance in tobacco cigarettes, nicotine delivery from electronic cigarettes is essential if these products are to be effective for smoking cessation or harm reduction. There are three key elements that influence nicotine delivery from e-cigarette vapour to human body: the nicotine content in the cartridge, which determines the amount of nicotine vapourised; the efficacy of vaporization, which affects levels of nicotine transferred from a cartridge into aerosol; and the bioavailability of nicotine, which determines the dose and speed of absorption of nicotine from the aerosol and subsequent transfer into the blood stream and hence to nicotine receptors in the brain.^[21] All of these characteristics vary across brands, manufacturers, and product designs.

Smoking a cigarette delivers nicotine throughout the lung and leads to absorption into both the systemic venous circulation from the oropharynx and large airways, and the pulmonary circulation from the small airways and alveoli. The latter route of absorption generates a rapid peak in systemic arterial nicotine levels and hence rapid delivery to the brain.^[22] No other nicotine product has yet been demonstrated to mimic the speed and high dose delivery characteristics of cigarettes. Since nicotine absorbed from the intestine is heavily metabolised on first pass through the liver, conventional nicotine replacement therapy (NRT) products rely on venous absorption from skin, nose or mouth, which avoid this hepatic metabolism but produce relatively low plasma levels, relatively slowly.^[23] It is not yet clear whether electronic cigarettes produce vapour that is sufficiently fine to reach the alveoli, but available pharmacokinetic data suggests that absorption is primarily from the upper airway, that is, slower than a cigarette, and achieving systemic venous blood levels of similar order of magnitude to a conventional NRT inhalator.^[24] Data on the arterial nicotine levels achieved by electronic cigarettes is not available.

It is also evident however that different electronic cigarette products are highly variable in the amount of nicotine they deliver in vapour,^[21, 25] and that the nicotine content indicated on a cartridge is not a reliable guide to likely nicotine delivery.^[25] Although there have been concerns that use of electronic cigarettes could lead to an overdose of nicotine, a study carried out using electronic cigarette brands available in the UK suggests that there is low risk of overdose of nicotine or even inhaling toxic doses of nicotine using electronic cigarettes.^[25] Newer generation PV devices may deliver higher doses of nicotine, but the absorption kinetics still indicate that absorption remains almost, if not completely, via the systemic rather than pulmonary vasculature.^[26]

2.3 Likely health effects relative to conventional cigarettes

The principal addictive component of tobacco smoke is nicotine. However, aside from minor and transient adverse effects at the point of absorption, nicotine is not a significant health hazard. Nicotine does not cause serious adverse health effects such as acute cardiac events, coronary heart disease or cerebrovascular disease,^[27, 28] and is not carcinogenic.^[29] The doses of nicotine delivered by electronic cigarettes are therefore extremely unlikely to cause significant short or long-term adverse events.

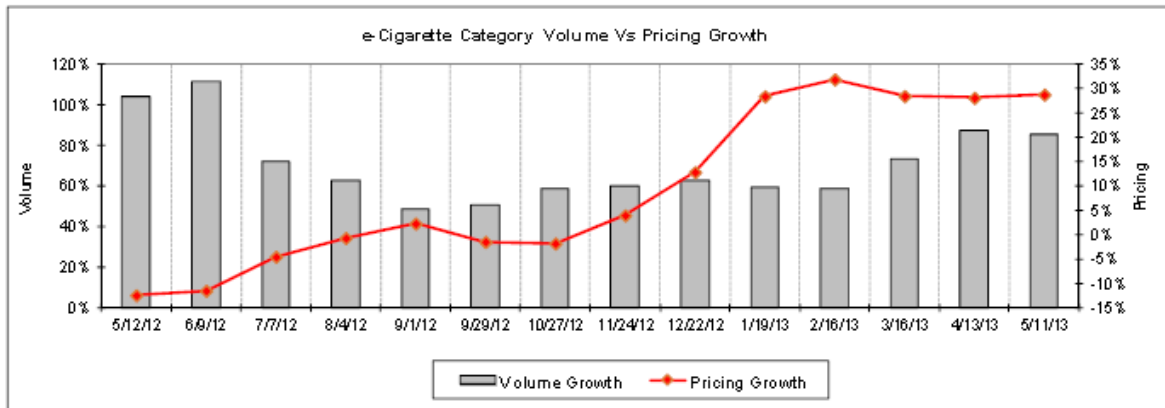
Cigarettes deliver nicotine in conjunction with a wide range of carcinogens and other toxins contained in tar, including nitrosamines, acetone, acetylene, DDT, lead, radioactive polonium, hydrogen cyanide, methanol, arsenic and cadmium,^[30] and vapour phase toxins such as carbon monoxide.^[7] In contrast, electronic cigarettes do not burn tobacco, so any toxins in vapour arise either from constituents and contaminants of the nicotine solution, and products of heating to generate vapour. The principal component other than nicotine is usually propylene glycol, which is not known to have adverse effects on the lung^[31] but has not to our knowledge been tested in models that approximate the repeated inhalation, sustained over many years, that electronic cigarettes involve. We are aware of two cases of lipoid pneumonia attributed to inhalation of electronic cigarette vapour, one in the peer-review literature^[32] the other a news report.^[33]

Despite some manufacturers' claims that electronic cigarettes are harmless there is also evidence that electronic cigarettes contain toxic substances, including small amounts of formaldehyde and acetaldehyde, which are carcinogenic to humans,^[34] and that in some cases vapour contains traces of carcinogenic nitrosamines, and some toxic metals such as cadmium, nickel and lead.^[34] Although levels of these substances are much lower than those in conventional cigarettes,^[34] regular exposure over many years is likely to present some degree of health hazard, though the magnitude of this effect is difficult to estimate.

2.4 Current trends in prevalence of electronic cigarette use

Worldwide use of electronic cigarettes has increased significantly over recent years, but varies markedly between countries. In a recent study carried out in four countries,

rates of ever use of electronic cigarettes were 15% in the US, 10% in the UK, 4% in Canada and 2% in Australia, typically with higher rates among younger age groups.^[35] In another representative study carried out in the US in 2010-11, 21% of adult smokers had ever used an electronic cigarette.^[36] Increasing use of electronic cigarettes in the US is also demonstrated clearly in data on trends in sales of electronic cigarettes which, in the US for example, demonstrated strong growth in volume and value of sales between 2012 and 2013 (figure 3).^[37]



Source: Nielsen C-Track Database and Wells Fargo Securities, LLC

Figure 3: Electronic cigarette market changes in the US (adapted from Wells Fargo Securities)

There is evidence that in the US, use of electronic cigarettes has become more popular among young people with ever use doubling between 2011 and 2012 from 3.3% to 6.8%, and current use increasing from 1.1% to 2.1%.^[38, 39] Most of this increase has occurred as a result of use by people who already use some form of tobacco product.^[38, 39] In a more recent analysis of 2011-12 data from young people in the US,^[40] reported widely (including by the British Medical Journal)^[41] to demonstrate gateway effects into smoking, use was again almost entirely restricted to young people who already smoked tobacco.^[40]

The most recent survey in the European Union (EU) demonstrates lower levels of use than in the US, with that in 2012, 7% of adults reporting in 2012 that they had tried an electronic cigarette, though most respondents reported awareness of the product.^[42] Data for the UK demonstrates trends in use similar to those in the US, with data from the Smoking Toolkit Study, a monthly survey of about 1800 adults including around 450 smokers, led by Professor Robert West at University College London.^[43] Data released in March 2014 demonstrates that electronic cigarette use, having increased rapidly over the past two years, has now stabilised at around 17%.^[44] *Action on Smoking and Health* (ASH) has estimated that currently about 1.3 million people in the UK use electronic cigarettes, and around 400,000 people have completely replaced smoking with electronic cigarettes.^[45] Electronic cigarettes are primarily used by current and former smokers, and only about 0.5% of never smokers in Great Britain have tried the product.^[46] Use of electronic cigarettes is equally common across age and socioeconomic groups.^[47]

3. Harm reduction

3.1 What is harm reduction, and how does it apply to tobacco use?

Harm reduction is a strategy used widely in health policy to reduce harm to an individual or society by modifying hazardous behaviours that are difficult, and in some cases impossible, to prevent. Examples include requiring drivers to wear seatbelts, promoting safer sexual practices, providing methadone to opiate addicts, and needle exchanges to reduce the risk of blood-borne infection in intravenous drug users.^[48]

Harm reduction policies have not to date been widely used in tobacco control, in which policies have to date tended to be centred on promoting complete cessation of all tobacco and nicotine use, with harm reduction limited to the introduction of cigarette filters, and (largely discredited) limits on machine-smoked tar yields. While this overall approach has achieved substantial success, with smoking prevalence having fallen among adults from 45% to 20% over the past four decades,^[49] the current 20% prevalence translates into about ten million smokers at immediate and sustained risk of premature death and disability. Conventional tobacco control approaches have by definition failed in these people, for whom harm reduction approaches, to minimise health harms until complete cessation can be achieved, are essential. The options for harm reduction in tobacco control include cutting down on smoking, use of modified cigarettes, smokeless tobacco products, nicotine replacement therapies, and more recently electronic cigarettes.

3.1.1 Cutting down on smoking

Cutting down on smoking, that is, reducing the number of cigarettes smoked each day, has been popular among smokers to reduce harm caused by cigarette smoking. However, smokers who cut down typically compensate by changing their smoking behaviour to extract higher doses of nicotine (and hence tar) from the cigarettes they smoke, by taking more and/or deeper puffs of smoke from each cigarette.^[50] This, and the fact that the exposure-response curves for harm are not all linear (for example, for cardiovascular disease risk increases dramatically with just one cigarette per day),^[4, 51] means that cutting down on the number of cigarettes smoked per day does not lead to proportionate reductions in harm to health, if indeed to any.^[52-55] There is benefit from cutting down on the number of cigarettes smoked, but this arises primarily from the fact that those who do so are more likely to make a quit attempt in the future.^[56]

3.1.2 Modified cigarettes

Modified cigarettes, sometimes referred to as potentially reduced exposure products (PREPS) have been promoted by the tobacco industry as an option to reduce risk. Low tar and low nicotine cigarettes, which promised enjoyment of smoking and lower risk to

health^[57] were an early example of this, though in practice the low tar yields were achieved by technologies such as filter ventilation which reduced machine-measured tar yields rather than 'real life' tar delivery, and were in any case undermined by compensatory smoking.^[50] Marketed as an alternative to quitting,^[57] low tar cigarettes proved to be counterproductive to public health.

In addition to conventional filters, which may have led to a modest reduction in cancer risk,^[58] other potential modifications include more effective (activated charcoal) filters, and heating rather than burning tobacco.^[59-61] To date however, non-combustion products have not proved commercially successful, and the extent to which minor reductions in toxin exposure translate into tangible reductions in health hazard to smokers remain far from certain.

3.1.3 Smokeless tobacco

Smokeless tobacco products, usually in the form of oral tobacco or nasal snuff, are widely available and used around the world. Although some are associated with significant health harms, including increased risks of nasal, oral or gastrointestinal cancer, none causes lung cancer or COPD and all are substantially less hazardous than smoked tobacco.^[62] Since smokers who switch from smoked to smokeless tobacco substantially reduce the hazard to their health from tobacco use, smokeless products have great potential as a harm reduction option for smokers. The least hazardous smokeless tobacco product in widespread use is Swedish snus, an oral product that has been used in Sweden for decades.^[62] However, with the exception of Sweden, supply of snus or similar products is prohibited throughout the European Union.

3.1.4 Nicotine replacement therapies (NRTs)

NRT comprises a group of medicinal nicotine products intended for use by smokers as a substitute for tobacco while attempting to quit smoking. Historically their use has been recommended in a reducing dose schedule over about three months from quitting smoking, but NRT products are also effective as a short- or long- term substitute for tobacco, that is, as a harm reduction option. UK medicines regulators have approved NRT for harm reduction indications including cutting down on smoking through dual use (which often leads to complete smoking cessation)^[63] and as a temporary or long-term abstinence from smoking, and in 2013 the National Institute for Health Care Excellence (NICE) issued guidance recommending use of NRT as a harm reduction substitute for smokers who are not ready or able to quit all tobacco and nicotine use.^[27, 64] However, NRT products have been designed to deliver low doses of nicotine, and most products to do so relatively slowly, in relation to absorption from cigarettes.^[23] This, and the fact that the products can be expensive relative to cigarettes at the point of sale, provide few if any of the behavioural characteristics of cigarettes that contribute to addiction,^[7] lack social acceptability as an alternative to smoking, and medicalise the act of trying to quit smoking, limits their attractiveness to smokers.

3.1.5 Electronic cigarettes

Electronic cigarettes offer nicotine delivery in a format that mimics smoking, have a socially acceptable non-medical image which enables users to retain their smoker identity but without the risk of smoke, are relatively inexpensive (start-up costs can be high, but running costs much lower than smoking), and despite (to date) nicotine delivery that is low relative to cigarettes,^[24] have proved popular with the current minority of smokers who use them. Consumer support for the product is evident from the user sites that a brief internet search on electronic cigarettes or vaping generates. To our knowledge, no users of NRT have ever felt sufficiently passionate about the product to establish a user website. Unlike NRT therefore, and particularly if nicotine delivery can be improved to mimic that of cigarettes more closely, these products have the potential mass appeal to challenge the primacy of smoked tobacco as the product of choice for nicotine users.

3.2 Evidence on effectiveness of harm reduction approaches

The experience of the availability of snus in Sweden provides a unique natural experiment in the impact of a socially accepted, non-medical, affordable and easily accessible reduced harm product on the prevalence of tobacco smoking.^[62] Snus is an oral moist tobacco which contains relatively low levels of tobacco specific nitrosamines^[65] and has a risk profile that includes possible increases in risk of oesophageal and pancreatic cancer,^[66] and of fatal (but not non-fatal) myocardial infarction,^[67, 68] but not COPD or lung cancer.^[62]

Although over recent decades the prevalence of any tobacco use has changed little in Sweden,^[65] the prevalence of smoking in Sweden, which has fallen from 30% in the 1980s^[69] to 13% today,^[42] is now the lowest in Europe. This in part reflects the effect of existing smokers switching to snus, and partly the effect of new tobacco users initiating snus use but not smoking.^[62, 65, 70, 71] One result is that Sweden now has an extremely low and decreasing lung cancer mortality rate.^[72] Similar trends and effects on smoking prevalence have been observed in Norway, where use of snus is a much more recent phenomenon, and both snus use has risen and smoking prevalence fallen markedly since the year 2000 (figure 4):

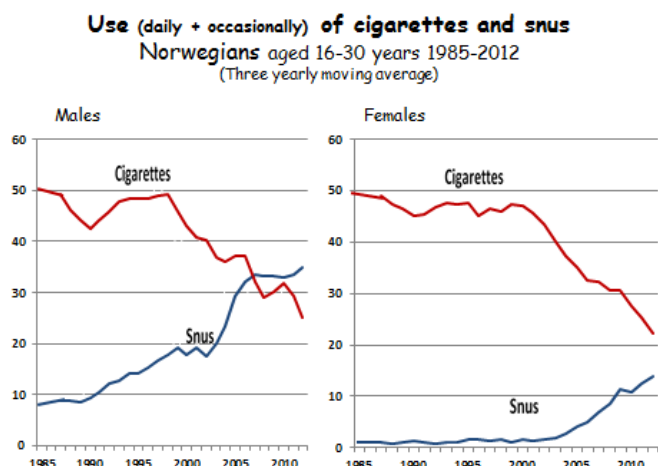


Figure 4: Trends in use of cigarettes and snus in Norwegian adults 1985-2012 (data presented to the Society for Research on Nicotine Conference 2013, figure provided by lead author)^[73]

Although controversial, the Swedish natural experiment demonstrates that despite dual use and primary uptake of the reduced-harm product by young people, availability of reduced-harm alternatives for tobacco smokers can have a beneficial effect. While snus is not likely to become a legal or indeed politically viable option in the UK, this data proves the concept that harm reduction strategies can contribute to significant reductions in smoking prevalence.^[62]

3.3 Where does harm reduction fit into UK policy and practice

Although historically in the UK, NRT was licensed for smoking cessation only, over recent years licencing regulations have become more relaxed, and in 2009 the UK Medicines and Healthcare products Regulatory Agency (MHRA) approved an extension to include harm reduction as an indication for the *Nicorette* inhalator, and suggested extending this indication to other nicotine containing products.^[74] In recent NICE guidelines, which cover licensed nicotine-containing products, long term use of medicinal nicotine has been recommended to help with quitting smoking, cutting down on smoking, or temporary abstinence.^[64] Harm reduction was also promoted in tobacco control white papers produced by both the previous Labour administration^[75] and the current coalition government.^[76] Many of these changes were encouraged in a report by the Royal College of Physicians, published in 2007.^[7] Harm reduction was also endorsed by Action on Smoking and Health in 2008 report endorsed by over 60 national organisations.^[77] In these respects UK tobacco policy leads the world. No other country, to our knowledge, has embraced the concept of harm reduction so strongly.

3.4 How do electronic cigarettes fit into a harm reduction strategy

Electronic cigarettes emerged on the UK market at around the time of the 2007 Royal College of Physicians report, which advocated making alternative sources of medicinal nicotine available to smokers as a competitive and non-medical alternative to tobacco. The rapid uptake of electronic cigarettes since then, despite uncertainties over their

purity and performance, demonstrates that, as has been the case with Swedish snus, many smokers welcome the availability of choice in nicotine products, and if provided with products that are attractive, affordable and easily available, will use them either in conjunction with, or in the longer term instead of, tobacco cigarettes. Electronic cigarettes also appeal to smokers by mimicking the sensation and appearance of smoking a cigarette, and by their market positioning as lifestyle rather than medical products. Electronic cigarettes, and the various new generation nicotine devices in development, clearly have potential to reduce the prevalence of smoking in the UK. The challenges are to harness that potential, maximise the benefits, and minimise risks.

4. Potential hazards of electronic cigarettes

As use of electronic cigarettes is a relatively recent phenomenon and evidence to date is scarce, there are still some major concerns about these products: those related to product itself, those about relation between use of electronic cigarettes and smoking, and concerns about renormalization and regulation of electronic cigarettes.

4.1 Hazards from the product itself

Potential hazards of electronic cigarettes relate primarily to the purity of nicotine emissions, and the effects of long-term exposure to vapour. Evidence on these is summarised in section 2.3 above, but relate primarily to the effects of substances other than nicotine in the vapour. Overall however the hazards associated with use of products currently on the market is likely to be extremely low, and certainly much lower than smoking. They could be reduced further still by applying appropriate product standards.

Electronic cigarettes do not produce smoke so the well-documented effects of passive exposure of others to cigarette smoke^[9, 10] are clearly not relevant. Exposure of non-smokers to electronic cigarette vapour poses a concern, though laboratory work suggests that electronic cigarette use in an enclosed space exposes others to nicotine at levels about one tenth generated by a cigarette, but little else^[78]. The health risks of passive exposure to electronic cigarette vapour are therefore likely to be extremely low.

4.2 Potential hazards, unintended consequences, harms to public health

Electronic cigarettes have caused controversy among public health professionals due to three main reasons: concerns about the relation between smoking and use of electronic cigarettes; regulations on advertising and promotion of electronic cigarettes; and involvement of the tobacco industry.

4.2.1 The relation with smoking

There have been some suggestions that among non-smokers, electronic cigarettes might be used as a gateway to smoking and promote smoking uptake and nicotine addiction, particularly among children and young people. However, to date there is no data supporting this claim. Experimentation with electronic cigarettes among non-smoking children in the UK is currently rare, and only about 1% of 16 to 18-year-old never smokers have experimented to electronic cigarettes and few if any progress to sustained use.^[47] Furthermore, experimentation with electronic cigarettes should be considered in the context of current levels of experimentation with tobacco cigarettes, which in Great Britain currently generates a prevalence of smoking of 15% among 16 to

19-year olds, and 29% in 20 to 24-year olds.^[79] Experimentation with electronic cigarettes is most likely to occur predominantly in the same group that currently experiment with tobacco, as indeed is suggested by recent US data.^[40] It is therefore relatively unlikely that availability and use of electronic cigarettes causes or will cause significant additional numbers of young people to become smokers than do at present. It has been suggested that there is a risk of sustained dual use among smokers who might otherwise have quit smoking completely, representing missed opportunities to achieve complete cessation. This concern clearly applies equally to NRT, which is licensed for what is in effect dual use and recommended on the grounds that dual use is likely to increase quit attempts. The concern is therefore inconsistent; if dual use is good as a pathway to quitting, that surely applies to dual use involving either NRT or electronic cigarettes.

Some argue that use of electronic cigarettes, which to a degree resembles cigarette smoking, in places where smoking is currently prohibited might re-normalize smoking and undermine tobacco control efforts.^[80] However, although similar in appearance, even cigalike products are easily distinguishable, both in appearance and smell, from tobacco cigarettes. Therefore, use of electronic cigarettes in smoke free places is more likely to lead to normalisation of nicotine devices than to smoking, and hence potential benefit as a support to existing well smoke-free policies.

4.2.2 Advertising and promotion

A potential greater concern over the similarity in appearance between the use of electronic and tobacco cigarettes relates to advertising, sponsorship, celebrity endorsement and portrayals in film and other media. In this area there is considerable scope for promotion of nicotine use to young people, representing a significant concern. Advertising will be controlled in future by developments in regulation of these products (see below), and the Committee of Advertising Practice is currently consulting on restricting the advertising of electronic cigarettes. Marketing of electronic cigarettes is covered in further detail in the parallel paper to this one, produced by Professor Linda Bauld.

4.2.3 Involvement of the tobacco industry

Although originally developed and marketed independently from the tobacco industry, all of the four transnational tobacco companies now own at least one electronic cigarette product, or has competitor products in development. In addition to sharing the commercial gains from electronic cigarettes, the tobacco industry is no doubt eager to exploit opportunities for advertising and promotion that might increase either electronic or tobacco cigarette use, and also, by becoming involved in the production of alternatives to smoking, circumvent current restrictions on engagement in policy imposed by the Framework Convention on Tobacco Control (FCTC).^[81] Given the ethical record of tobacco industry activity in promoting and defending smoked tobacco, this is an obvious and significant potential threat, but also one that needs to be

addressed across the board as all nicotine suppliers are driven primarily by commercial rather than public health interests. While those commercial and public health interests largely coincide in the promotion and sale of electronic cigarettes to smokers, they do not in the non-smoking population. This is a key argument for regulation to prevent abuse of the electronic cigarette market.

5. Potential benefits of electronic cigarettes

The potential benefits of electronic cigarettes lie in their role as a reduced-hazard competitor for cigarettes.

5.1 Who uses electronic cigarettes and why?

The great majority of the more than one million users of electronic cigarettes in the UK are current or former smokers.^[46] Most users use them to either replace cigarettes in places where smoking is prohibited or discouraged, to cut down on smoking, to reduce harm from smoking, or to quit smoking.^[20] As the nicotine delivery kinetics of electronic cigarettes improves with technological developments, these products may prove to be more effective than conventional NRT as a tobacco substitute as their physical and behavioural characteristics replace many of the co-stimulatory factors that contribute to nicotine addiction.^[7] Availability in convenience stores, competitive pricing, non-medical image and social acceptability also probably contribute significantly to use. Prevalence of use is similar between genders and socio-economic groups, though higher in younger than in older smokers.^[20, 46]

According to the Smoking Toolkit Study, use of electronic cigarettes is much more common among heavier smokers and ex-smokers (figure 5), and more recent ex-smokers report current use of electronic cigarettes than conventional NRT (figure 5).

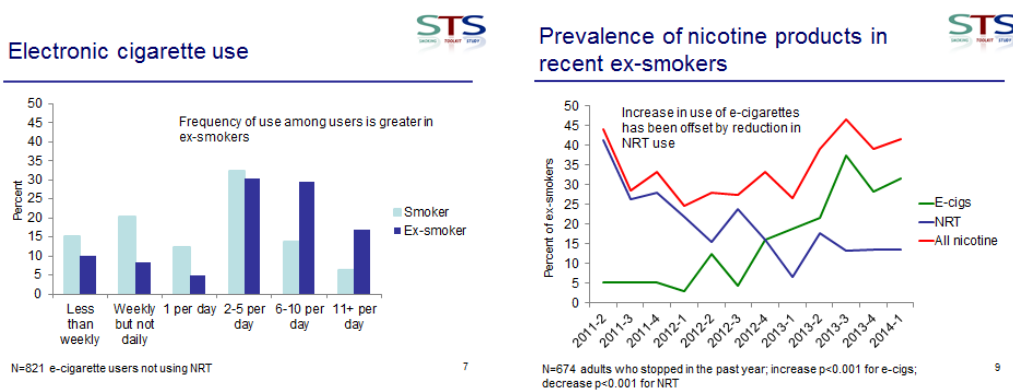


Figure 5: Use of electronic cigarettes by current and ex-smokers (left panel) and of nicotine products in recent ex-smokers (right panel; data from Smoking Toolkit Study[44])

The increase in electronic cigarette use over recent years appears to reflect in part, smokers using electronic cigarettes instead of NRT; and in part, users who would not otherwise have used NRT. This is particularly true of smokers attempting to quit, among whom electronic cigarettes are now the first choice. In this group, increasing

use of electronic cigarettes has been associated with reductions in numbers using NHS stop smoking support, or buying over-the-counter NRT, but there has also been an increase in the total number of smokers using any form of support to quit (figure 6). The net result appears to be an increase in the proportion of smokers who have quit within the past year (figure 6).

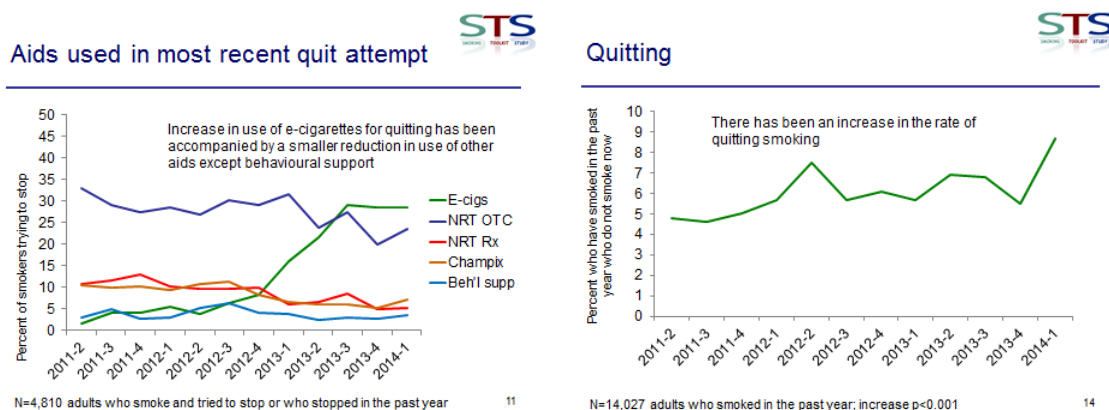


Figure 6: Aids used in most recent quit attempts (left panel) and proportion of smokers who have quit in the past year (right panel; data from Smoking Toolkit Study[44])

5.2 Effectiveness of electronic cigarettes as cessation aids

Evidence from clinical trials on the effectiveness of electronic cigarettes is limited, though results from observational and randomised trial data suggests that efficacy of first generation electronic cigarettes is similar to that of the transdermal NRT patches^[82] or the *Nicorette* NRT inhalator^[24]; findings that are consistent with the apparently low dose delivery and upper airway absorption of early generation products. Low nicotine delivery, or just the non-nicotine behavioural components of electronic cigarette use may explain why, in a trial comparing electronic cigarettes used to deliver either a constant nicotine dose, or a reducing dose, or no nicotine over 12 weeks demonstrated a decrease in tobacco consumption in all groups, but little difference between them.^[83] An observational study has also documented significant reductions in smoking among smokers with schizophrenia using electronic cigarettes.^[84] A recent study revealed that about 6% of former smokers who used electronic cigarettes daily relapsed to smoking after one month, and 6% after one year, and nearly a half of dual users stopped smoking after one year, indicating that electronic cigarette use might be effective in relapse prevention and smoking cessation.^[85] Dual users who used electronic cigarettes to cut down on smoking have lower levels of respiratory symptoms which is likely to be due to reduced smoking.^[20]

These studies indicate that electronic cigarettes are moderately effective as smoking cessation and harm reduction aids, but that a significant component of that effect is due to the behavioural rather than nicotine delivery characteristics of the devices. However, most of the available evidence relates to early generation devices of unknown but

almost certainly low nicotine delivery. More recent and future devices may prove much more effective.

5.3 Population-level impact of electronic cigarettes

The most effective way to quit smoking is to use a combination of pharmacotherapy and behavioural support, as for example provided in England by NHS Stop Smoking Services (SSS). However, while a majority of smokers report that they want to quit smoking, less than 10% access SSS each year.^[86] Most smokers attempt to quit without help ('cold turkey') or use over-the-counter NRT; and now electronic cigarettes.

The advantage of electronic cigarettes in this context is that, as shown in figure 6, they result in more smokers using some kind of medication or substitute for cigarettes to quit, and this appears to be increasing the proportion of smokers who quit. However the probability of quitting successfully without behavioural support, even with some form of nicotine replacement, is much lower than the quit rate among people who use SSS.^[87] Although this may reflect differences in motivation to engage fully with services, many of those who pass up on SSS to quit in other ways, and fail, represent missed opportunities.

Electronic cigarettes therefore increase smoking cessation to the extent that they draw in smokers who would not otherwise use a nicotine substitute in an attempt to quit, but reduce it to the extent that they take smokers away from SSS. The optimum solution for population health is to maximise both the use of electronic cigarettes among smokers, and the proportion of users who engage with SSS. This will require some changes to current SSS practice.

6. Regulation of electronic cigarettes in the UK

6.1 Current UK regulation

Electronic cigarettes are currently marketed in the UK under general product safety regulations which do not impose specific standards of purity or efficacy, and control advertising through voluntary codes of practice,^[88] which are now being reviewed,^[89] but deal with breaches reactively, in response to complaints, rather than proactively, through pre-screening. Proponents of this approach maintain that it minimises regulatory barriers and costs to product development and innovation, and that freedom to advertise maximises reach across the smoking population. Opponents hold that general product regulation does not ensure that products deliver nicotine reliably or without unnecessary and potentially hazardous components or contaminants, and allows inappropriate marketing, for example, to children or to non-smoking adults.

6.2 UK MHRA regulation

In 2013, after a consultation process that began in 2010, the UK MHRA announced that from 2016, it intended to regulate electronic cigarettes and other nicotine-containing products as medicines by function, and thus require manufacture to medicinal purity and delivery standards, and proactive controls on advertising.^[88] The proposed regulation, described as 'right touch', is intended to provide a relatively streamlined route to licensing, particularly by deeming any nicotine device that is proved to deliver nicotine to be effective as a smoking substitute or cessation aid, thus obviating the need for expensive clinical trials. Manufacturing to medicines standards does however represent a challenge and inevitably increases costs. On the positive side however, licensed NRT products currently enjoy a preferential 5% VAT rate, which to some extent offsets these additional costs, and will benefit from being prescribable on NHS prescriptions in the UK. Proponents of this approach welcome the quality and delivery standards imposed, and the advertising controls which should prevent marketing abuses before rather than after the event. Opponents argue that this level of regulation will stifle innovation and delay development of innovative products that could save lives.

These MHRA proposals were published before the revision of the EU Tobacco Products Directive in 2014 (see section 6.3), one consequence of which is to close off the option of deeming all nicotine products as medicines by function. MHRA regulation will therefore no longer be obligatory in the UK from 2016, but option of applying for a medicines licence remains open.

6.3 EU regulation

In March 2014 the European Parliament and Council moved to end marketing under general product safety regulations under the terms of the new Tobacco Product Directive (TPD).^[90] Under this directive, advertising of nicotine-containing devices that are not licensed as medicines will be prohibited, products will be required to carry health warnings, meet purity and emissions standards that are yet to be defined, provide data on nicotine uptake, be subject to restrictions on total nicotine content, and suppliers will be required to bear full responsibility for quality and safety when used 'under normal or reasonably foreseeable conditions'.^[90] Dates for enactment are yet to be specified, but legislation is expected to be required in member states by 2016, and full compliance by 2017. In practice, this means that from 2017 at the latest, suppliers will have to choose between the probably lower manufacturing costs but greater marketing restrictions imposed by the TPD, or to accept the higher manufacturing costs but other benefits of medicines licensing.

7. New developments

7.1 Technological developments

This is a rapidly developing field, and although this article has dealt predominantly with electronic cigarettes, there are many other novel nicotine devices in development likely to come to market in the relatively near future. British American Tobacco, for example, is bringing to market (via a wholly-owned subsidiary company, *Nicoventures*), a novel 'cigalike' device that is a nicotine metered dose inhaler, not an electronic cigarette.^[91] Philip Morris has also invested in a patented novel nicotine device, and other tobacco companies, the pharmaceutical industry and indeed electronic cigarette companies may elect to do the same. It is therefore likely that over the near term future, in addition to improvements and developments in the performance of electronic cigarette technology, novel devices that have similar or greater potential to appeal to smokers, and offer significantly greater purity and efficacy, and a lower hazard profile, will become available.

7.2 Licensing developments

It is now apparent that companies intending to market electronic cigarettes are now going to have to meet either medicines or TPD regulations, and probably from 2017 at the latest. Until the current draft of the TPD was circulated, applications to the MHRA in the public domain were few, but more manufacturers may now be considering opting for the clarity, albeit at a cost, of medicines regulation rather than the uncertainty and advertising restrictions of TPD regulation. The *Nicoventures* inhaler product is expected to be licensed by the MHRA, and marketed in the UK, within the year, and the same company has also applied for a medicines license for an electronic cigarette.^[91] Other tobacco companies may follow suit, while pharmaceutical companies, concerned by the loss of over-the-counter sales of NRT to electronic cigarettes, may also decide to enter this market. It is thus likely that by this time next year, health professionals will be able to prescribe, and patients will be asking them for, prescriptions of novel nicotine products. Some of those are likely to be produced by tobacco companies or wholly funded subsidiaries.

8. Research priorities

The world literature on harm reduction practice is extremely limited. Such data as is available on the content and emission characteristics of products currently on the UK market has been produced almost entirely by independent researchers, not by suppliers. Absorption characteristics are virtually unknown. However, this is data that can and should be required of manufacturers or suppliers, and will be as a result of medicines or TPD regulation, but for up to three years will not be required. While a clearly important area of research, it seems inappropriate to use scarce public research funding to provide this data. This responsibility should be placed, as soon as possible, on suppliers.

There is also questionable value in clinical trials of these products relative to NRT or placebo, if they are shown to deliver nicotine. There is a mass of evidence demonstrating that products that deliver nicotine help people stop smoking, which is why the MHRA, in its proposal for medicines licensing, does not require trial information. Requiring suppliers to demonstrate nicotine delivery and uptake will therefore obviate the need for placebo-controlled trials.

However, at a population level there is no experience of proactive introduction of a harm reduction strategy based on provision of alternative nicotine products anywhere in the world, and hence no direct evidence on the practical benefits, harms, opportunity costs or consequences of this approach. The key requirement of harm reduction research, in our view, is to monitor and where necessary identify opportunities to intervene to ensure that uptake and use follow patterns most likely to benefit public health; and act to prevent loopholes or practices that run counter to this objective. Priorities in this regard therefore include:

- frequent surveys to monitor trends in use of harm reduction products, to enable prompt corrective action where necessary
- monitoring of advertising, product placement, celebrity endorsement, and other direct or indirect marketing approaches, to prevent promotion likely to work against public health (particularly, marketing to children and other non-nicotine users)
- surveillance and reporting systems to identify potential long-term adverse effects of use, both of nicotine and of the carriers (such as propylene glycol) used in these devices
- methods of integrating electronic cigarette or other nicotine devices into health services, in general and particularly in mental health settings, where conventional approaches have failed
- studies of the economic impact of electronic cigarettes on health and wider economic and societal costs

9. Summary and conclusions

Smoking kills, and millions of smokers alive today will die prematurely from their smoking unless they quit. This burden falls predominantly on the most disadvantaged in society. Preventing this death and disability requires measures that help as many of today's smokers to quit as possible. The option of switching to electronic cigarettes as an alternative and much safer source of nicotine, as a personal lifestyle choice rather than medical service, has enormous potential to reach smokers currently refractory to existing approaches. The emergence of electronic cigarettes and the likely arrival of more effective nicotine-containing devices currently in development provides a radical alternative to tobacco, and evidence to date suggests that smokers are willing to use these products in substantial numbers. Electronic cigarettes, and other nicotine devices, therefore offer vast potential health benefits, but maximising those benefits while minimising harms and risks to society requires appropriate regulation, careful monitoring, and risk management. However the opportunity to harness this potential into public health policy, complementing existing comprehensive tobacco control policies, should not be missed.

Declaration of interests

John Britton is professor of epidemiology at the University of Nottingham and an honorary consultant in respiratory medicine at Nottingham City Hospital. He is director of the UK Centre for Tobacco and Alcohol Studies, chairs the tobacco advisory group of the Royal College of Physicians, a member of the board of trustees of Action on Smoking and Health, and chairs a Public Health Advisory Committee for the National Institute for Health and Care Excellence (NICE). He receives salary from the University of Nottingham and honoraria for NICE work, and has no financial or other conflicts of interest.

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