https://doi.org/10.1038/s41591-022-02201-7

Nicotine e-cigarettes as a tool for smoking cessation

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There is abundant evidence that e-cigarettes can help some individuals to quit smoking, so they should be more widely recommended as smoking cessation aids.

Electronic (or e)-cigarettes are hand-held, battery-operated devices that heat a liquid — containing propylene glycol and/or glycerin, flavoring compounds, and typically nicotine — to produce an aerosol that users inhale, or vape. The consequences of nicotine vaping are controversial, with two perspectives dominating the discussion: the risks of vaping for young people; and the potential of vaping to increase smoking cessation among adults[1]. In this Comment, we focus on the latter. First, we review evidence that vaping increases smoking cessation. Then, we examine the health consequences of e-cigarettes. Next, we review differences across countries in how e-cigarettes are regulated. Finally, we conclude with what the evidence implies for clinical care, taking into account what medical and governmental authorities in various countries consider to be the appropriate role of e-cigarettes in smoking cessation.

Vaping and smoking cessation

Examining randomized controlled trials, a living systematic review in the *Cochrane Database of Systematic Reviews*[2] concluded that, "There was high certainty that [smoking] quit rates were higher in people randomized to nicotine [electronic cigarettes] than in those randomized to nicotine replacement therapy". The authors also found evidence of cessation benefits when comparing nicotine e-cigarettes with non-nicotine e-cigarettes, and with behavioral support or no treatment.

Population studies support the randomized controlled trial findings. Studies in both the UK and the US have associated increases in smoking cessation of 10–15% with the use of e-cigarettes. Studies have also consistently found that smokers who vape frequently are significantly more likely to quit smoking than are smokers who do not vape[1]. The US Centers for Disease Control and Prevention has reported that smokers are more likely to use e-cigarettes in quit attempts than any other product, including smoking cessation medications approved by the US Food and Drug Administration (FDA)[3], and with greater success[4]. E-cigarettes are also the most popular cessation aid in England, and are associated with greater success than other cessation aids when used in stop-smoking services[5]. That more smokers use e-cigarettes than licensed smoking cessation medications — presumably because of the availability of the former as consumer products — further increases the potential of vaping to reduce smoking. Simulation analyses have generally concluded that by increasing smoking cessation, vaping will avoid large numbers of premature deaths over time[1].

Market data provide additional evidence, demonstrating an inverse relationship between sales of cigarettes and of e-cigarettes.

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Table 1 | Variation in e-cigarette regulations internationally

Regulation	Estimated minimum number of jurisdictions implementing regulation	Examples of jurisdictions implementing regulation
Prohibition of sale of all e-cigarettes	39	Brazil, India, Iran, Mexico, Uganda
Pre-marketing authorization or notification for all or some e-cigarettes	42	EU, New Zealand, Papua New Guinea, Paraguay, UK, US
Ban on non-tobacco flavored e-cigarettes	6	China, Finland, Hungary, Lithuania, Netherlands, Ukraine
Ban on non-tobacco and non-menthol flavored e-cigarettes	2	Denmark, Estonia
Ban on nicotine-containing e-cigarettes	2	Jamaica, Japan
Restriction on nicotine content of e-cigarettes	39	Australia, Canada, EU, Iceland, Israel, Jordan, New Zealand, UK
Minimum age of purchase, sale, or use (at one of 18, 19 or 21 years)	56	Australia, Canada, Honduras, New Zealand, Norway, Republic of Korea, Turkey, Tuvalu, UK, US
Regulations prohibiting or regulating e-cigarette marketing	78	Albania, Australia, Canada, Costa Rica, EU, Iran, Nepal, New Zealand, Senegal, UK
Child-safety packaging regulations	38	Australia, Canada, EU, Iceland, Lithuania, UK, US
Health warnings on e-cigarette packaging	51	Australia, Canada, Egypt, EU, Greenland, Maldives, New Zealand, Republic of Korea, UK, US
Plain packaging	1	Israel (for all e-liquids)
Bans or restrictions on e-cigarette use in public places	66	Australia, Brunei Darussalam, Canada, Croatia, Ecuador, Jamaica, New Zealand, Togo
Excise tax on e-cigarettes	39	Canada, Costa Rica, Denmark, Ecuador, Germany, Indonesia, Norway

There is no data source that provides a comprehensive coverage of all countries' e-cigarette regulations, and so two sources are used: Johns Hopkins Global E-Cigarette Policy Scan, available at https://globaltobaccocontrol.org/en/policy-scan/e-cigarettes (this source indicated that the status of e-cigarette regulations in many countries was unknown); and Smoke-free Canada: Restrictions on E-Cigarette Flavors, July 2022, available at https://smoke-free.ca/SUAP/2021/e-cigarette-flavour%20restrictions.pdf. Only regulations that apply at a national level are included; countries that have adopted these policies in some but not all states or provinces or communities are not included. Although the third column gives examples of jurisdictions having adopted each relevant regulation, Australia, Canada, the European Union (EU), New Zealand, UK and US are included in all instances in which they have adopted the regulation.

As the popularity of e-cigarettes grew in the US, cigarette sales declined at a more rapid rate than in the pre-e-cigarette era. Conversely, when e-cigarette sales have declined, cigarette sales have approached the more gradual rate of decrease experienced prior to the introduction of e-cigarettes[1]. Consistent with this pattern, studies by economists provide convincing evidence that cigarettes and e-cigarettes are substitutes for each other[6].

Support for this conclusion that cigarettes and e-cigarettes are substitutes comes from research finding that policies intended to restrict e-cigarette use may have unintentionally increased cigarette smoking. A Minnesota tax on e-cigarettes was associated with increased cigarette smoking and reduced cessation among adults[7]. Studies of youths' responses to e-cigarette taxes have similarly found that, although the taxes decrease the use of e-cigarettes, they increase the use of combusted cigarettes, particularly by increasing frequent smoking[8].

Much less harmful

Although e-cigarette use is not harmless, both the US National Academies of Sciences, Engineering, and Medicine[9] and an independent review commissioned by the Department of Health and Social Care in England[5] have concluded that e-cigarette use is likely to be much less harmful than smoking.

A comparison of cigarette smoke and e-cigarette aerosol helps to explain why. Cigarette smoke includes more than 7,000 chemicals, including 70 known human carcinogens. The number of chemicals in e-cigarette aerosol is orders of magnitude lower, and toxicants common to both products are present in much lower concentrations in e-cigarette aerosol. Human biomarker studies confirm that exposure to tobacco smoke toxicants is much lower with e-cigarette use than with cigarette smoking. Although nicotine is the addictive agent common to both products, chemicals other than nicotine cause nearly all of cigarette smoking's health risks[5,9].

The two best-described adverse effects of e-cigarette use are nicotine addiction among young people who have never smoked cigarettes, and a risk of pulmonary symptoms. In 2022, 6.5% of young people from US high schools reported vaping on 20 or more days per month[10], suggestive of nicotine dependence; but most were current or former cigarette smokers, many presumably already addicted.

Studies exposing cells and animals to e-cigarette liquids or aerosols demonstrate some harmful pulmonary effects, but it is difficult to extrapolate these effects to human exposures[11]. In young people, pulmonary harms related to vaping include bronchitis symptoms and aggravation of asthma. However, among adults with asthma or chronic obstructive pulmonary disease, switching from cigarettes to e-cigarettes reduces symptoms and improves lung function, indicating a reduction in harm[12]. In addition, exclusive users of e-cigarettes (most of whom are former smokers) report fewer respiratory symptoms than do cigarette smokers and dual users. Whether vaping causes long-term pulmonary toxicity is difficult to determine, as most vapers are former smokers and few have used e-cigarettes long enough to develop chronic obstructive pulmonary disease.

The risk to cardiovascular health of using e-cigarettes is of concern owing to nicotine exposure and evidence of chronic inflammation and

Table 2 | Recommendations for healthcare professionals

Status	Guidance	Source	Message
For a person who smokes tobacco	Advice to patients about e-cigarette benefits and risks[a]	Authors	E-cigarettes can help some people to stop smoking combustible cigarettes.
			Using e-cigarettes is substantially less harmful than continuing to smoke cigarettes, but e-cigarettes are not completely harmless. Questions remain about their health effects, especially if used long-term.
	Recommendations about how to use e-cigarettes for smoking cessation	Authors	If using e-cigarettes to quit smoking, a person should switch completely to e-cigarettes, use them regularly, and stop smoking all cigarettes as soon as possible.
			When switching from cigarettes to e-cigarettes, a person may experience a period of using both products, known as dual use, during a transition period prior to complete smoking cessation. With dual use, the greater the reduction in cigarettes smoked, the greater the likelihood of reduced risk. However, long-term dual use means that the dangers associated with cigarette smoking will not be completely avoided.
			E-cigarettes are likely to be most effective when accompanied by a behavioral support program, as is true when smoking cessation medication is used.
			Because of the uncertainty about the risk of using e-cigarettes long-term, former smokers should plan to quit e-cigarettes eventually but only when they are confident that they will not go back to smoking combustible cigarettes.
			People should not tamper with commercial e-cigarette products.
			Side effects or safety concerns should be reported to a healthcare professional and to governmental health authorities. For example, in the UK, they should be reported through the Yellow Card system. In the US, they should be reported to the Food and Drug Administration (FDA).
	Guidance from medical organizations and government agencies	US and Canada	Persons seeking an aid to quit smoking should first use products that have been medically licensed as safe and effective smoking cessation aids. These include nicotine-replacement products, varenicline, and bupropion.
			Individuals who are unable to quit smoking with government-approved medications should discuss with their healthcare professional the risks and benefits of using e-cigarettes to reduce their smoking-related health risks. Healthcare practitioners and professional organizations vary in their comfort about, or willingness to recommend, e-cigarettes to smokers. Many healthcare professionals will initiate a conversation and recommend e-cigarettes to selected smokers.
			US healthcare professionals should be aware that the US FDA has authorized the marketing of several e-cigarette brands as consumer products on the grounds that their public health benefits outweigh harms. This implies that the FDA believes that some e-cigarettes will help a subset of people to quit smoking who would not do so otherwise. However, the FDA has not licensed any e-cigarette as a smoking cessation medication.
		England and New Zealand	Patients seeking to quit smoking should have access to a choice of products that includes e-cigarettes, several licensed medications, and behavioral support programs.
			Healthcare professionals should give clear, consistent, and up-to-date information about nicotine-containing e-cigarettes to adults who are interested in using them to stop smoking, and advise patients about how to use e-cigarettes.
		Australia	E-cigarettes are not considered first-line treatments for smoking cessation. Individuals who have tried unsuccessfully to quit smoking using approved medicines should speak to their doctors about whether e-cigarettes containing nicotine are a suitable option. Doctors can prescribe nicotine-containing e-cigarettes for their patients who smoke.
For a person who does not smoke tobacco	Advice to patients about e-cigarettes	Authors	People of all ages who do not use any combustible tobacco products should be discouraged from using e-cigarettes. E-cigarette use is not completely harmless to health and can lead to nicotine addiction for people not using any other nicotine products.

[a]Our advice is consistent with guidance from public health agencies in the US, UK, Canada and New Zealand, but not Australia. Australia's National Health and Medical Research Council states: "E-cigarettes can be harmful". Australia's government website states: "Even though scientists are still learning about e-cigarettes, they do not consider them safe"; "Currently, there is insufficient evidence to promote the use of e-cigarettes for smoking cessation"; and "They are sometimes marketed as a way to quit smoking, but there's not enough evidence to show that they help — or are safe."

oxidative stress found in some human biomarker studies. Nicotine is not thought to cause atherosclerotic heart disease or strokes, but could promote ischemia and acute cardiovascular events in people with pre-existing cardiovascular disease[13]. Some human experimental studies report that acute e-cigarette use impairs endothelial function (a feature of cardiovascular disease), akin to smoking. However, when smokers quit smoking and switch to e-cigarettes, endothelial function improves, indicating harm reduction[14].

Reproductive toxicity is a concern with any nicotine-delivery device. Nicotine impairs the maturation of the fetal brain and lungs in animals. Cigarette smoking is associated with small-for-gestational-age newborns, and a greater risk of preterm delivery. E-cigarette use during pregnancy has been studied both in those who choose to vape (instead of smoking) and in pregnant women provided with e-cigarettes to aid smoking cessation. Birthweight outcomes are conflicting in different studies[15,16]. In any case, given the far greater exposure to toxicants in cigarette smoke, it seems likely that exclusive vaping during pregnancy should be less harmful than smoking. Of course, abstinence from all nicotine and tobacco products is preferable.

Given the relative novelty of vaping, its long-term health risks cannot be assessed directly. However, existing evidence suggests that potential long-term harms are likely to be substantially less than those associated with smoking.

Contrasting regulations

Country-specific approaches to regulating e-cigarettes range widely. Table 1 illustrates the diversity of national policies, providing examples of countries with each policy and indicating the minimum number of countries known to have implemented each. Policies range from restrictions on e-cigarette flavors to outright prohibition of e-cigarette sales, from marketing regulations to restriction of nicotine content, and from taxes on e-cigarettes to laws on minimum age of sale.

At least 42 countries use an authorization or notification system before products can be marketed. The US and UK provide two examples that demonstrate the differences in these systems and how those differences affect the number and variety of e-cigarettes accessible to consumers.

The US authorization process requires companies to submit detailed Premarket Tobacco Product Applications to the FDA to seek a Marketing Granted Order that permits a nicotine-containing e-cigarette to continue to be sold or brought to market. As of November 2022, out of millions of these applications filed with the FDA, only 23 e-cigarette products from two tobacco companies and one independent company had received such orders, and these permitted tobacco flavors only. Numerous applications remain under review, and many e-cigarette products remain on the market, pending review or enforcement of Marketing Denial Orders.

By contrast, the UK Medicines and Healthcare products Regulatory Agency (MHRA) runs a notification system for nicotine-containing e-cigarettes[5]. This involves manufacturers submitting a range of details on their products, with those e-cigarettes that comply with certain standards (such as nicotine strength, additives, and packaging) being allowed on the market. Since January 2021, more than 15,000 e-cigarette products and e-liquids with a wide variety of flavors have been notified to the MHRA database, where retailers and consumers can check whether products are legally allowed on the market. New Zealand has a similar notification process to that of the UK[5].

At present, no country has a medicinally licensed e-cigarette for smoking cessation, although many countries have mechanisms for enabling licensing. In the UK, the MHRA recently updated its medicinal licensing process for e-cigarettes to clarify the processes involved and to encourage manufacturers to pursue a license[5]. In the US, for authorization for smoking cessation, an e-cigarette would have to go through the FDA's stringent drug approval process, managed by the Center for Drug Evaluation and Research. Approval requires that drugs are deemed safe and effective. Although all approved drugs have some potential undesirable side effects, this standard could pose a problem for e-cigarettes, as they likely involve some health risks, albeit far less than do cigarettes. In Australia, a physician's prescription is required for all nicotine e-cigarettes, which are not permitted to be sold as consumer products.

Clinical care

On the basis of scientific studies and governmental reports and policies, professional medical organizations synthesize evidence about e-cigarettes and translate it into clinical guidance for healthcare professionals involved in smoking cessation. Guidance provided by both government agencies and medical societies varies, falling into two broad groups.

In the US[17] and Canada, government agencies acknowledge a potential benefit of e-cigarette use but conclude that the evidence to recommend e-cigarettes for smoking cessation is insufficient at present. Uncertainty about long-term health effects also tempers the agencies' enthusiasm for e-cigarettes. Reflecting this ambivalence, neither government agencies nor major medical organizations in the US, Canada or Australia recommend e-cigarettes as first-line cessation aids, instead prioritizing governmentally licensed pharmacotherapies. Many but not all US and Canadian medical organizations regard e-cigarettes as appropriate to consider for smokers who are unsuccessful when trying to quit with licensed pharmacotherapies. Views of healthcare professionals and medical organizations vary as to whether healthcare professionals should actively initiate a discussion of e-cigarettes, or respond only if a smoker asks about them.

By contrast, government health agencies and professional societies in England and New Zealand interpret the evidence of e-cigarette effectiveness for cessation and the risk–benefit balance more favorably, encouraging healthcare professionals to consider e-cigarettes as a cessation option on a par with medicinally licensed pharmacotherapies and behavioral support. Both countries have featured e-cigarettes in government-funded public education campaigns promoting smoking cessation. Both countries exhort healthcare professionals and stop-smoking programs to make e-cigarettes readily accessible for adults who smoke, along with medicinally licensed products and behavioral interventions. Both countries also provide specific guidance on how to use these products to achieve optimal outcomes.

The cautious tone of professional and government guidance in the US and Canada has limited healthcare professionals' enthusiasm to recommend e-cigarettes for cessation. The FDA's recent market authorization of several e-cigarette devices is an opportunity to reassure US healthcare professionals. The authorizations mean that the FDA has concluded that the approved brands are "appropriate for the protection of the public health"[18] — the standard they are required to meet to receive approval for marketing. This action implies indirectly that the FDA believes that e-cigarettes can help some individuals to quit smoking who would not do so otherwise. Were some e-cigarettes medicinally licensed, healthcare professionals would have further reassurance and better guidance to help patients to choose appropriate devices and liquids and to use them effectively and safely.

Table 2 summarizes our interpretation of desirable clinical practice on the basis of existing evidence and differences in specific countries' positions on e-cigarettes.

A smoking cessation tool

Vaping of most newer-generation e-cigarettes results in the delivery of nicotine to the lungs in a manner similar to that of cigarettes[19]. These e-cigarettes pose a risk of nicotine addiction for some young people, but for adults already addicted to cigarettes — the single deadliest consumer product ever invented — they also serve as an important, less-hazardous alternative to continued smoking. Considerable evidence indicates that e-cigarettes help some adults to quit smoking.

Having engaged in substantial research into vaping, each of the authors of this Comment respects the approach adopted by governments and medical professional bodies in England and New Zealand.

Further, we believe that governments, medical professional groups, and individual healthcare professionals in countries such as the US, Canada and Australia should give greater consideration to the potential of e-cigarettes for increasing smoking cessation. E-cigarettes are not the magic bullet that will end the devastation wrought by cigarette smoking, but they can contribute to that lofty public health goal. However, acceptance of the promotion of e-cigarettes as a tool for smoking cessation will likely depend on continuing efforts to reduce access to, and use of, the products by young people who have never smoked. The two objectives can and should co-exist[20].

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Published online: 13 February 2023

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Acknowledgements

A.M. is a National Institute for Health and Care Research (NIHR) Senior Investigator. The views expressed in this article are those of the authors and not necessarily those of the NIHR, or the Department of Health and Social Care.

Competing interests

N.L.B. serves as a consultant to pharmaceutical companies that market or are developing smoking cessation medications, and has provided expert testimony in litigation against tobacco companies. N.A.R. consults with and has received a research grant from Achieve Life Sciences for development of a smoking cessation medication, and receives royalties from UpToDate (an online medical textbook) as author of sections on e-cigarettes.