Electronic cigarettes: How bad are they for your health?

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Tobacco smoking remains one of the major risk factors of morbidity and mortality. Pathogens within tobacco smoke induce inflammatory processes which in turn lead to cancer, lung and cardiovascular diseases [1] including stroke [2]. Smoking cessation is therefore a priority for healthcare systems worldwide, and numerous strategies to support smokers on their journey to a smokefree life have been developed over the years.

Electronic cigarettes (ECs) are battery-powered devices that simulate smoking by vapourising an "e-liquid" which is inhaled in the form of an aerosol. Over recent years there has been rapid technological progress including changes in device size and battery power, paralleled by an ever-growing number of e-liquids for sale. ECs are a product in its own right but are often consumed in addition to tobacco smoking or in an attempt to reduce the number of tobacco cigarettes consumed and ultimately to quit smoking [3]. While conventional nicotine replacement therapies (NRTs; *e.g.* oral, transdermal or inhaled nicotine) help to reduce the craving for cigarettes associated with smoking cessation, they cannot fully substitute for the sensation of cigarette smoking that includes behavioural and social aspects as well as taste. The smoke-like taste of some e-liquids and the rapid absorption of nicotine from vaping are thought to make ECs an ideal replacement for tobacco cigarettes. While ECs have indeed been shown to facilitate smoking cessation, superiority of ECs compared to NRTs toward complete cessation has not been demonstrated [4].

Whilst the harmful effects of cigarette smoking are widely documented, the health effects of ECs are less clear. In 2018, Public Health England concluded that "risks of cardiovascular disease and lung disease have not been quantified but are likely to be also substantially below the risks of smoking" [5]. However, due to the relative novelty of ECs there are still no long-term human data available, and only few robust clinical and preclinical studies have systematically dissected the physiological and pathophysiological aspects of vaping; further research is required.

There are unique challenges related to EC research (Figure). First, the rapid development of EC technology is a challenge to the slower pace of thorough scientific work. Newer ECs are more effective at delivering nicotine but also of other potentially harmful substances and thereby fundamentally different from first generation devices. Research on a third or fourth generation EC cannot be directly compared with data generated in first or second generation devices. Second, there is a large number of e-liquids available on the market, not including e-

liquids that are prepared by customers themselves. Whilst some constituents such as propylene glycol, glycerine and nicotine are common across most e-liquids, added constituents and flavourings can be vastly different and come with additional toxicity potential. It may not be unreasonable in epidemiological research to group ECs and e-liquids into broader categories and in basic research to focus on the main constituents of e-liquids but obviously even small levels of specific additives have the potential to cause harm. Third, as a result of the vapourising process there is a fundamental difference between the composition of an e-liquid and the composition of the inhaled aerosol, amongst others depending on the temperature of the vapouriser and the type of EC used. A relatively small number of e-liquid constituents translates into a much larger number of substances in the aerosol, some of which are toxic and have carcinogenic potential, even if it has been argued that their number and concentration is lower than that in tobacco cigarette smoke [6]. Fourth, as with any research into environmental exposures, short and long-term effects may be different; local and systemic effects need to be studied; and preclinical *in vivo* and *in vitro* models may not fully represent human pathophysiology. Finally, apart from their chemical effects, the presumed relative safety of ECs has paved their way into vulnerable populations, including children and adolescents where EC use has been found to serve as gateway to future use of marijuana and illicit drugs [7].

The recent reports on an outbreak of deaths associated with the use of certain e-liquids and EC brands in the United States [8] has raised concerns about their safety and sparked interest in EC-related research. As of January 14, 2020, there have been 2668 cases of e-cigarette, or vaping, product use associated lung injury (EVALI) have been reported to Centers for Disease Control and Prevention with 57 confirmed deaths [9]. Whilst the majority of EVALI may be associated with customizing specific constituents (such as tetrahydrocannabinol (THC) and Vitamin E acetate) in e-liquids sold in the United States [9], it illustrates the complexity of EC research outlined above, including regulatory aspects (in Europe vitamins must not be added to e-liquids, whereas few regulations currently exist in the United States) as well as the complex chemistry involved (oral vitamin E is not normally associated with harm but may have different effects when inhaled as part of an EC aerosol or combined with other chemicals).

What has been found to be challenging for EVALI research also applies to cardiovascular and other systemic effects of ECs, with the additional complexity that systemic effects depend on uptake from the alveolae into the pulmonary capillaries. Model systems cannot fully represent human biology and especially in complex conditions such as cardiovascular diseases there are limitations of preclinical studies. The current knowledge of cardiovascular effects of ECs has been recently summarised by Buchanan *et al.* in this journal [10] and we would only mention three exemplars to illustrate the direction of research in this area. First, while model systems may not fully represent human biology (especially in complex conditions such as cardiovascular diseases), they do provide an opportunity to study chronic exposures that can serve as a harbinger for humans. In an 8-month study on mice, smoking and vaping produced similar impairment in endothelium-dependent vasodilation and increased aortic stiffness, suggesting that long-term vascular consequences may not be different between daily cigarette versus EC use [11]. This study mimics 25 years of exposure in humans but still comes with the general limitations of preclinical research mentioned above. Second, human exposure studies are difficult to conduct due to ethical constraints related to exposure to potentially harmful substances. Short-term exposure studies have, however, shown changes in extracellular microparticles and vascular function assessed by pulse wave analysis and peripheral arterial tonometry [12] and elegantly in a wider range of vascular beds by 3T-MRI [13], even in the absence of nicotine. Longer term functional studies and biomarker research is urgently needed in humans. Third, we need a better understanding of the components of EC aerosol that could cause harm. A recent study reported induction of lung adenocarcinomas and bladder urothelial hyperplasia in mice exposed to aerosol from an e-liquid containing only nicotine, isopolypropylene glycol and glycerine [14] which points towards potentially harmful effects even of the basic constituents of e-liquids – even in the absence of nicotine [13]. Additive effects of flavours on carcinogenesis or cardiovascular diseases remain incompletely understood.

In summary it is probably reasonable to believe that ECs are safer than tobacco cigarettes with respect to cancer, and perhaps even in the development of emphysema, however short-term exposure studies in humans and emerging preclinical data do not suggest the same toward cardiovascular outcomes. Even where ECs are used as smoking cessation tool the overall public benefit remains controversial, especially when weighed against a growing generation of children and adolescents that will be shackled to nicotine addiction with the preconception that ECs are safe. Lack of data and misinformation can even contribute to the

uptake of ECs by non-smokers due to the perception that they are not harmful – a risk that reminds the medical and scientific community to communicate research findings precisely and correctly [15]. Indeed, the emerging cardiovascular risks cannot be ignored.

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Figure: Challenges in e-cigarette research.

A large number of differently composed e-liquids is vapourised by different types of e-cigarettes. This process has the potential to generate additional potentially toxic and carcinogenic substances that were not present in the original e-liquid. This aerosol comes in contact with the respiratory system and some of the molecules in the aerosol will then be absorbed into the blood stream and further distributed to all tissues and organs. Effects on all these systems can be acute and/or chronic. Icons made by Freepik and Vitaly Gorbachev from www.flaticon.com.

Biosketch C Delles

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Biosketch I Mark Olfert

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