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A narrative review evaluating the safety and efficacy of e-cigarettes as a newly marketed smoking cessation tool

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Abstract

Introduction: E-cigarettes are an alternative to traditional tobacco-based cigarettes. While having considerable societal awareness, conflicting evidence exists to support their claims that they are an effective smoking cessation tool and are safe. Currently >7000 flavours exist with evidence that they exhibit detrimental cellular and tissue effects. A literature review was conducted utilising PubMed and Google Scholar Databases identifying papers between 2014 and 2019. The aims of this study were to accurately gauge the safety and efficacy of e-cigarettes as a smoking cessation tool.

Methods: Search terms including 'electronic cigarettes' and 'vaping' were used to identify suitable references. A total of 314 articles were identified from which papers were excluded due to risk of bias, insufficient detail or were duplicate from which 58 papers were used in the final review.

Results: Evidence shows that e-cigarettes can have detrimental effects on several cell lines and animal models with their flavourings and nicotine content implicated; this has, however, not translated into major health outcomes after 3.5 years follow-up but has been linked to chronic lung disease and cardiovascular disease. While advertised as an effective smoking cessation tool, no consensus can be made regarding their effectiveness although the first robust randomised controlled trial reports some success. This, however, is offset by the fact that the most common e-cigarette use is as a dual user and that there is evidence of threefold increased risk of future tobacco smoking.

Conclusion: Future research is needed to evaluate the long-term health outcomes and efficacy of e-cigarettes as a smoking cessation tool with greater discussion between patients and clinicians regarding this smoking cessation tool.

Keywords

E-cigarettes, electronic nicotine delivery system, safety, smoking cessation, vaping

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Introduction

Tobacco has been socially accepted since its introduction into Europe by Christopher Columbus. At present, the burden of tobacco use is highest in developed countries; however, it is lower in developing countries where its use is predicted to rise. At present, smoking is the world's single most leading preventable cause of death, being linked to the development of several conditions including lung cancer, chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD). As such many rules and regulations exist to protect members of society from this dangerous habit by limiting its sale, purchase and use.[1,2]

While many health agencies promote smoking cessation and smoking prevalence has reached its lowest in 50 years, it remains a substantial problem. Cross-sectional surveys estimate that up to 19%–21% of the US population continue to smoke.[3,4] Indeed, while smoking cessation is an important objective for clinicians and their patients, it is increasingly becoming apparent that nicotine replacement therapy (NRT) is often unsuccessful, with up to 93% of individuals relapsing within 6 months of initiating therapy and fewer than 5% individuals abstinent at 1 year without the use of pharmacotherapy.[3,5] As such new and efficacious ways are being sought to sustain smoking cessation in at-risk groups, thereby limiting future health problems.

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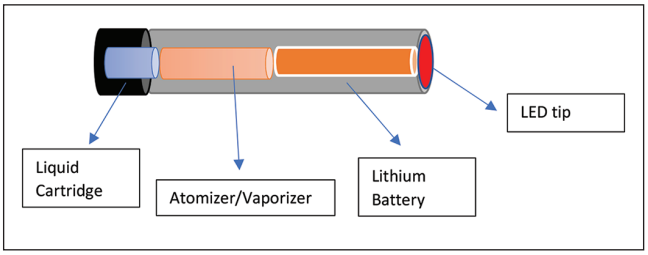

Figure 1. Components of the e-cigarette.

E-cigarettes are types of electronic nicotine delivery systems (ENDs) that were first conceived in 1963 to curtail smoking-related deaths while delivering the pleasures of smoking that users enjoy. However, it was not until 2003 that the first generation of e-cigarettes came into production with fourth-generation units now existing. The basic e-cigarette contains three main elements (Figure 1).[6] First, a lithium battery, second an atomiser (heating element) which vaporises the carrier fluid (e-liquid) and third a reservoir which contains the e-liquid. Activation of the heating element within the atomiser is responsible for the nicotine aerosol which is then inhaled.[6] It is now being appreciated that e-cigarette vapour contains high concentrations of particular matter (PM) although less than conventional cigarettes. These have found to range considerably in size from micrometres to nanometres with evidence that they are able to penetrate with relative ease to the alveoli of the lung where they can induce inflammation and translocate into the bloodstream.[7] In addition, the risks of second-hand smoke (SHS) which we can consider synonymous to the e-cigarette aerosol refers to smoke that persists in the environment while third-hand smoke (THS) is environmental smoke that persists for long periods due to adsorption to surrounding surfaces. It is these exposures that have led to concern regarding their private/public use especially as there is evidence of an age–exposure relationship.[8]

At present, many governments around the world are struggling to regulate this modern technology as more and more people embrace it with conservative estimates placing 2.1 million e-cigarette users in the United Kingdom alone.[9] While providers marketing e-cigarettes have perpetuated the idea of a safe, inexpensive smoking cessation tool, a paucity of studies exist regarding their safety and efficacy in this regard. For example, one of the few systematic reviews that exist on the subject conducted in 2014 included only six studies of which only two were randomised controlled trials (RCTs) with such differences in the quality of evidence limiting the results applicability and value.[10] Indeed, the US preventive services task force, an independent body founded on disease prevention and evidence-based medicine, found that there is insufficient data to recommend them as a smoking cessation tool.[11] Unlike many other counties, the UK Royal College of Physicians (RCOP) and Public Health England have advocated e-cigarettes as a smoking cessation aid with the latter citing that they are 95% less harmful than tobacco cigarettes although they accept various caveats to this with major international criticism ensuing following this announcement.[12,13] More worrying is their growing popularity in previous non-smokers and youth populations with whom the various flavours, their psychopharmacological properties and social acceptance as a 'healthy' alternative to cigarette smoking attract. Currently, it is thought up to 10% of youths and 6% of American adults have sampled e-cigarettes with their use high particularly in lesbian, gay, bisexual, and transgender (LGBT) and poor young adults and heaviest in heavy current tobacco smokers with 70% of e-cigarette users also smoking cigarettes and thus hindering any of their potential health benefits.[6,12,14] E-cigarettes are only now facing regulation both in the United States and Europe. This is following several reports that have challenged both their safety and efficacy. Prior to this they were freely available from online and market vendors with over 400 brands and >7000 flavours of e-cigarettes now thought to exist each with a very different chemical profile and constitution.[15] As such, clear knowledge of the evidence and toxicology of these agents is required by the responsible clinician, who is likely to encounter their use within patients of different specialities, and in those who wish to stop smoking.[16]

It is because of this meteoric rise in popularity of e-cigarettes that as a profession we are playing catch up trying to synthesise evidence regarding an already marketed product. Given the marked divergent views regarding the role and efficacy of e-cigarettes as a smoking cessation tool that exists, the need for clear data regarding their safety and efficacy is needed as well the role if any they may hold in smoking cessation. This will allow for proper patient and clinician education and the correct categorisation of this product and avoid any associated harms. This narrative review will consider these issues and the need for further regulation and investigation of the safety of e-cigarettes as both a healthier alternative to tobacco smoking and as a smoking cessation tool which is an area thus far that is lacking.

Methods

Literature search was conducted for this narrative review in April 2019. Papers were identified through a literature search utilising Google Scholar and PubMed databases. Papers were selected if they were written in English and were published in peer-reviewed journals between 2014 and 2019. Articles were only included if they dealt with either the safety of e-cigarettes or the efficacy of e-cigarettes as a smoking cessation tool. Search terms included 'electronic cigarettes' OR 'e-cigarettes' OR 'electronic nicotine delivery system' OR 'Vaping' AND 'efficacy', OR 'toxicity' OR 'smoking cessation' OR 'safety'. These terms were used in isolation and combination to locate search results.

Following these search terms, 312 articles were found from which screening of study designs and study aims by both authors were conducted through title and abstract analysis. Further references were found from their respective reference lists. Any and all queries raised during this process

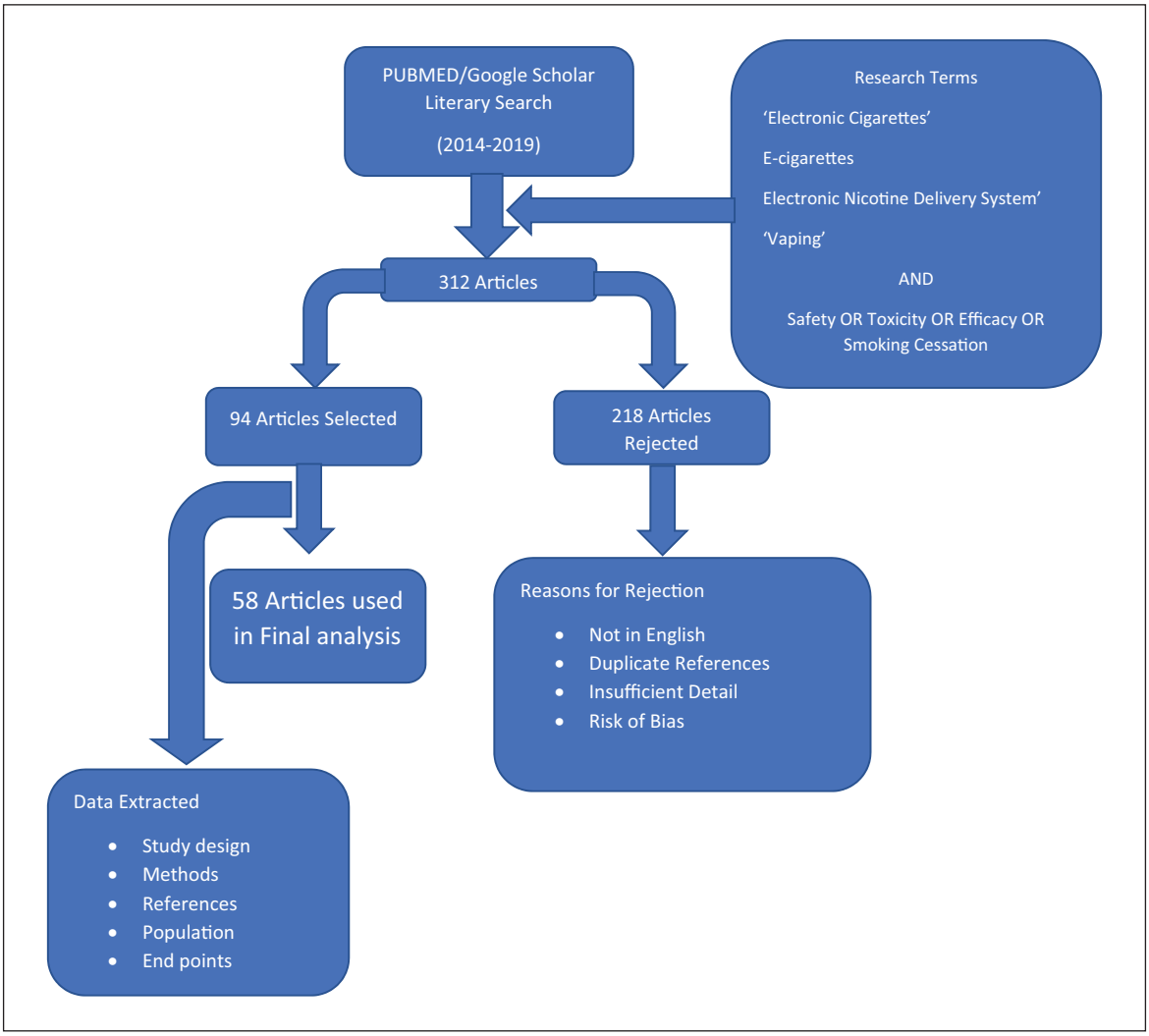

Figure 2. Methods of literature review.

regarding the manuscripts were dealt by contacting the paper authors for clarification. Papers were excluded if they were not written in English, had duplicate references or study populations, insufficient detail, were not peer-reviewed or did not adequately explore the safety and/or efficacy of e-cigarette use. Application of these criteria reduced the literature yield to 94 articles for full-text analysis. Data extracted from this analysis included population, end points, follow-up, study design and methods. After assessment of papers based on article strength and relevance in answering this reviews' aims with removal of papers with a conflict of interest, publication/selective bias and overlapping patient/outcome data, 59 papers were selected for the narrative review (Figure 2).

Results and discussion

Safety

While many claims have been made that e-cigarettes represent a healthier option to traditional tobacco-based cigarettes, there have been few studies that have informed this judgement. Particularly, the matter of how much less harmful they may be and what long-term effects if any exist.[17] This is something to be addressed as there are predictions e-cigarettes use will supersede conventional tobacco use within the next 10 years.[18]

The role of e-cigarettes is perpetuated by the tobacco companies who own them as a method of harm reduction. However, it is accepted first that their interest is profit and not public health based and second that no amount of tobacco reduction other than cessation offers health benefit. This is an important point as e-cigarettes have bypassed the usual manner of phased trials to licensing and as such there is ongoing work to try and understand the place that they may have within public health.[19]

When considering the toxicity profile of e-cigarettes, it is important to consider that the contents of the 'e-liquids' is seldom characterised or disclosed by the manufacturers. Moreover, it has been noted that significant e-liquid variation exists within units of the same manufacturer including

reported nicotine content; with nicotine contents of >100 mg/mL freely available for purchase.[20,21] When a user draws on the e-cigarette, the atomiser is activated which heats the e-liquid and produces a vapour at temperatures ~350°C. The constituents of the e-liquid, namely, propylene glycol, glycerol and nicotine have high boiling points (188°C, 290°C and 247°C, respectively). As such the vapour seen is an aerosol of microscopic liquid droplets with the appearance of smoke.[22] Thus, we have the main difference between these two products, in tobacco-based cigarettes toxicant exposure is due to inhalation of smoke by burning tobacco while in e-cigarettes it is due to inhalation of a heated aerosol which as mentioned can result in significant environmental exposures as both SHS and THS.[23] It is of no surprise therefore due to the high temperatures achieved by the atomiser and the unstable nature of the lithium battery particularly on overheating that cases of e-cigarette explosion have been noted, including reports of spontaneous explosion without recent use.[24] In one retrospective and perspective view of e-cigarette-related injury in two major UK burns centres between 2015 and 2016, it was found that males were more likely to suffer burn-related injury (92% of cases), the most common site of burns injury was the thigh (83%) with average total body surface area of the burn being 2.54% taking on average 23 days to heal fully with conservative management.[25]

While this fundamental difference exists with regard to the breath in products, serum cotinine levels, a metabolite of tobacco, are found in similar levels in active and passive e-cigarette smoking as in conventional tobacco smoking.[26] Both types of smoking produce up to 10^{15} free radicals and heavy metal nanoparticles per puff. These latter products are likely to originate from the e-liquid container itself or from the heating of the vaporiser and as such is dependent on several parameters chosen by the user including voltage of the atomiser, e-liquid choice and depth of inhalation and can penetrate deeply into the lungs and cross the pulmonary blood barrier. These metal nanoparticles are implicated in reactive oxygen species (ROS) formation which can cause single strand breaks in DNA and mutagenesis.[27] This, however, remains important for dispelling the notion that the vapour of e-cigarettes is effectively water.

Other toxic substances that have been described in e-cigarettes are also by-products of the heating process. These include heavy metals (e.g. cadmium, lead), toxic carbonyl compounds (e.g. formaldehyde and acetaldehyde), volatile organic compounds and tobacco-specific nitrosamines (TSNAs). The concerns with this is the fact that all three of these are carcinogenic compounds and while present in e-cigarettes exist at lesser levels (9–450 times lower) than in tobacco-based cigarettes although nicotine content may be significantly higher in what has been branded a 'risk free' alternative.[15,26] Moreover, the vehicle fluids, for example, propylene glycol and glycerine, have been shown to impair lung function through increased respiratory impedance and can be associated with dry throat and cough and in some cases airway obstruction with an objective reversible reduction in forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) ratio of 3% having been noted upon acute use. Unsurprisingly, this could be more significant in patients who have background COPD/asthma.[20]

Other common acute side effects of e-cigarette use include nausea, headache, cough and mouth/throat irritation and airway hyperactivity. However, conventional cigarettes have been reported to suppress tobacco withdrawal as well as reduce carboxy-haemoglobin levels within 2 weeks of initiation.[6] In addition to the above, case reports are beginning to circulate adverse events particularly in the elderly upon acute exposure with cases of new-onset pulmonary atrial fibrillation and myocardial infarction as well as relapse of ulcerative colitis.[26] Such events can have significant ramifications for the patient and as such personalised risk stratification may be needed in patients when counselling them regarding e-cigarette use.

Increasingly, there have been reports of nicotine overdose in users and in infants in whom fatalities have been recorded. This reflects not only the growing popularity of e-cigarette smoking but also the elevated and highly incongruent levels of nicotine found within e-cigarettes of even the same brand and the fact that nicotine may be absorbed through several routes including inhalation, ingestion and transdermal. Indeed, when an e-cigarette user exhales, the vapour may be deposited onto surrounding surfaces as THS and it is by this route that significant exposure may occur in children. This is something that has been investigated in the car environment where passive smoking is a high risk to children and other passengers with propylene glycol and nicotine values found to exceed safety levels.[14,18,28]

It is of note that nicotine while important in mediating addiction has been found to affect diverse cellular and tissue behaviours including proliferation, apoptosis and epithelial-mesenchymal differentiation culminating in cytotoxicity in human cell assays. This is important as these same processes are deregulated in cancer, however, at present; nicotine is not seen as a carcinogen as studies involving NRT have failed to demonstrate an increased cancer risk.[29,30]

At present, nicotine concentrations vary from 0% to 5% within e-liquids and members of the public can tailor this alongside flavour choice. We know that the uptake of nicotine from traditional NRTs appears to be slow with a lower peak and less sustained plasma peak concentration versus conventional tobacco cigarettes. The first study looking at the pharmacokinetic properties of e-cigarette nicotine was conducted in 2010, which showed that in first-generation e-cigarette devices peak plasma nicotine levels after 5 min exposure were 10 times lower than that of tobacco cigarettes but was associated with reduced cravings. In addition to this, it has been found that smokers naive to e-cigarette use are less able to achieve the same maximal values as those users experienced in their use. This is because of patient behaviours

such as puffing intensity and frequency but interestingly not puff frequency. It should be added that since the development of successive models of e-cigarettes, higher nicotine yields can be attained as they can be with increasing e-liquid nicotine concentrations. It is thought that it can take up to 20 minutes to achieve similar peak values as compared to tobacco smoking. However, there is great variability in the methodologies used in those studies assessing the pharmacokinetics of nicotine in e-cigarettes. If this can be standardised, then better e-cigarette products could be designed to achieve the pleasures of smoking while reducing concurrent tobacco use.[31]

A relevant discussion is what effect e-cigarette use may have in patients with pre-existing COPD or chronic exposure to tobacco. This is important as these are among the most important patients to impress upon the need to successfully stop smoking and where conversations surrounding e-cigarettes may take place. This is also important as the airway epithelium provides the first site of exposure in e-cigarette smoking and it is here where tissue remodelling can lead to progressive chronic lung disease. Recent studies in e-cigarette toxicity demonstrate that their vapour can enhance oxidative stress and inflammation and impair immune defence against bacterial and viral infection.[3] This is in part because their use promotes biofilm formation which can lead to increased risk of pneumonia and bronchitis in an already at-risk group due to increased antibiotic resistance and virulence gene expression explained by the process of quorum sensing.[32] More recently, it has been shown that e-cigarettes can induce pathogenic responses within the lung not dissimilar to COPD within a mouse model. This is in part because of nicotine's ability to induce smooth muscle proliferation and enhance neutrophil activity with the degree of emphysematous change related to the nicotine content of the e-cigarette.[3] This is of concern for two reasons: first, due to conservation of proteins and immune responses, it is likely these effects will be seen in humans; second, COPD is a major source of morbidity and is associated with the need for long-term oxygen and premature mortality. So, while e-cigarette use may reduce the future risk of lung cancer, it may result in progressive worsening of existing and development of chronic lung disease. Indeed, epidemiologically, evidence exists to support that e-cigarette use is associated with the development of asthma although a causal link remains elusive.[16] One RCT investigating the pulmonary effects of e-cigarette smoking over 1 year showed that measures of obstruction and airway inflammation (flow at 25%–75% FVC; nitric oxide levels; carbon monoxide levels) were amenable to change within 3 months with those who completely abstained from tobacco able to normalise both their carbon monoxide (eCO) and nitric oxide levels (FeNO).[33] A further trial looking at health outcomes over a 3.5-year period in 16 patients who were daily e-cigarette users with less than 100 tobacco cigarette lifetime use showed that there were no detectable changes in lung function, FeNO or eCO. Unlike many other studies, they employed imaging with high-resolution computed tomography (HRCT) which revealed no changes associated with early lung damage such as micronodule and ground glass formation. While an important study demonstrating the relative safety of their use with regard to lung function, it was limited by its small sample size and the length of follow-up as tobacco smoking-related lung disease can take decades to present itself; however, it does avail some concerns regarding their use.[34] CVD is another major source of mortality in tobacco smokers; while acute exposures to e-cigarettes are linked to increased heart rate and blood pressure, ongoing research has considered looking into long-term cardiovascular risks particularly as most e-cigarette users are dual users. Utilising Behavioural Risk Factor Surveillance System Surveys (BRFSS) and analysing over 400,000 people, it shows that dual users have an increased likelihood of CVD versus tobacco cigarette users (odds ratio (OR), 1.36). The mechanism of this increase could be linked to platelet activation, altered hemodynamics and oxidative stress.[35]

As e-cigarettes have become more popular, ever diverse flavours have been developed to incentivise their use and mask the bitter taste of nicotine. There are to date >7000 flavours most of which have been deemed safe by the Flavour Extracts Manufacturers Association (FEMA) for ingestion but not inhalation. Indeed, it is this lack of established safety that has raised concerns and prompted investigations into their health effects upon inhalation. It is these flavouring agents which are hypothesised to cause the greatest amount of harm and are cited as a significant reason for e-cigarette initiation and continues use in users.[12,36]

Indeed, in a recent review of 30 flavoured e-cigarettes in nearly half of those tested the flavourings analysed made up $>1\%$ of the weight of the e-liquid, highlighting the importance in characterising the chemical structure of these flavours. Of those analysed, the majority were aldehydes which are known respiratory irritants and may be carcinogenic and 69% contained diacetyl, a known cause of popcorn lung.[37] Another study assessing the toxicities of commonly used flavours found that cetoin (butter), pentanedione (pine), diacetyl, maltol (malt), ortho-vanillin (vanilla), coumarin and cinnamaldehyde all had different effects on human bronchial epithelial cells (Beas2B), human lung fibroblasts (H292) and transformed lung epithelial cells (HFL-1). All flavours were able to induce significant increases in interleukin (IL)-8 levels, a potent pro-inflammatory cytokine in all cell lines bar HFL-1 cells without causing changes to cell viability. How this IL-8 release is achieved is postulated to involve mitochondrial dysfunction and the formation of ROS. Importantly, in this study, toxicity observed was not due to nicotine use, highlighting that nicotine free e-cigarettes are also important mediators of local and systemic inflammation noted in cellular/animal models of e-cigarettes with the flavouring used the likely

culprit.[36] A more recent study evaluating the biological effects of e-liquids (flavoured and non-flavoured) on normal human bronchial epithelial (NHBE) cells showed them to be ~100 times less toxic and biologically active than cigarette smoke condensate. In addition, nicotine free e-liquids containing propylene glycol/vegetable glycerine at high concentrations have no effect on cell viability.[38] This article highlights an important fact that e-liquids upon vaporisation can produce toxic compounds which do not exist in the liquid form and that one must take this into account when testing them in in vitro assays.

A key question is whether the inflammatory reaction to e-cigarette vapour is specific to airway cells or not. One study looking at the effects of 11 flavouring agents on human umbilical vein endothelial cells (HUVECs) found that 5 were able to reduce cellular proliferation for up to 48 h post-exposure. Unsurprisingly, those flavours which elicited the highest rates of quiescence also were the most cytotoxic in nature and were either berry or herbal based and did not contain nicotine. This finding has been replicated in several studies in HEK293T cells, human embryonic stem cells and mouse neural stem cells. The method by which this cytotoxicity was achieved, however, did not seem to be ROS-based, suggesting alternative methods of toxicity and appears to be independent of nicotine concentration.[38,39]

One major issue for healthcare providers to consider is the potential use of e-cigarettes within pregnant women. Currently, it is commonplace for obstetricians to enquire about smoking practices in pregnant women; however, up to 40% never ask about non-combustible tobacco products and up to 42% of American obstetricians believe e-cigarettes are safer or have no health effects.[40] This is an important consideration as women are more likely to try e-cigarettes than men, and up to half of all pregnancies are unplanned.[39] Even so, this remains the most likely point in a woman's life of successful smoking abstinence (~40%). This is due to the considerable public and professional awareness that tobacco cigarette use is associated with suboptimal perinatal and obstetric outcomes. How this occurs is thought to be secondary to carbon monoxide–mediated hypoxia and nicotine-mediated vasoconstriction of the placental vasculature.[41]

Nicotine has been shown to quickly reach the foetal brain upon inhalation in the pregnant women. Here, it binds to the predominant types of nicotinic acetylcholine receptors (nAchR) ($\alpha 7$ and $\alpha 4\beta 2$) which are implicated in foetal brain maturation but also cell survival and neural tract organisation and migration.[4,16] It is during this time where the development of mature neural circuitry is taking place that the brain is most vulnerable to exogenous nicotine exposure. Such early exposure has been associated with both structural and biochemical changes within the brain which can occur at much lower doses than needed to retard general growth.[40,41] In addition to binding to nAchRs in the brain, nicotine can bind to nAchRs in the lung and result in reduced surface area to volume ratio and emphysematous lung lesions. In addition, offspring exposed to nicotine have been found to have elevated blood pressure, increases in body weight and predisposition to diabetes in later life. In addition, there appears to be evidence of multigenerational effects of nicotine exposure, with significant changes in lung function and protein expression within the fibroblasts of rats in two successive generations post exposure. As such, screening practices must change in pregnant women, as the risks to the unborn child and future generations seem higher than first thought.[41,42] Moreover, compared with adult exposure to nicotine, adolescents are more likely to have reduced executive function dysfunction and increased impulsivity and as such may be more inclined to test other substances with nicotine acting as a 'gateway' substance.[18]

While these studies offer some idea of the general side effects of nicotine content within e-cigarettes on the developing foetus, only a few experimental models have tried to assess the congenital abnormalities that e-cigarettes may cause. Early studies in zebrafish have associated their use with structural heart defects and functional aberrations including delayed onset of beating with reduced expression of late markers of cardiac maturation at achievable vaping concentrations. Work in *Caenorhabditis elegans* has suggested that oxidative stress is the likely mechanism by which disrupted organogenesis takes place making e-cigarettes dissimilar to tobacco-based cigarettes in this regard.[43,44] Smoking is well known to increase the risk of craniofacial disorders as well as a myriad of other deformities. In one study looking into the effects of vaping exposure in *Xenopus laevis* (African claw frog), results showed that banana pudding, cinnamon, menthol and kola flavours were all able to cause craniofacial deformities but had differential toxicity when used in human embryonic stem cells.[45] As such further studies are required to detail the expected side effects of e-cigarette use within pregnancy so that women can be appropriately counselled as currently screening practices for e-cigarette use in pregnancy are lacking.

Given this wide-ranging evidence of possible harm, it is unsurprising that there is confusion from the medical profession regarding e-cigarette use which can affect their confidence in exploring this subject with patients. In one qualitative study looking at the view of different members of the Australian multidisciplinary team from surgeon, anaesthetist, nurse and so on regarding e-cigarette use, there was a universal lack of awareness and experience in discussing the use of e-cigarettes.[8] This is something that has been highlighted in several papers on the subject. Indeed in one study conducted in South Carolina (USA), all physicians from several specialities agreed that they are aware that there is a general lack of scientific evidence in recommending them but uncertain what evidence does exist reporting they would look to patients raising the issue of e-cigarette use rather than they themselves raising it highlighting this apparent lack of knowledge.[46] One UK study involving 150 clinicians at all levels of training from consultant to core trainee highlighted

that in the United Kingdom where a proactive stance towards e-cigarettes has been advocated by Public Health England that the majority strongly (73%) felt that e-cigarettes were much healthier than tobacco smoking with 68% reporting that they would recommend e-cigarettes to their patients although not as a first measure with only 40% of respondents ever having been asked about e-cigarettes. This does highlight that clinicians feel more comfortable when prominent organisations in their country have offered a recommendation regarding a technology's use. In addition, it highlights that with e-cigarettes there are both patient- and physician-associated factors that are influencing both discussing them in the clinical environment with the mutual lack of knowledge most certainly being a factor and requiring further investigation.[47]

To summarise those studies that have tried to assess their toxicology in humans are often of low power, cross-sectional in nature and often study short-term exposure in e-cigarette naïve patients. Furthermore, in studies that have attempted to uncover serious side effects, a lack of standardised means of testing exists to compare e-cigarettes with their more studied tobacco-based counterparts. There is a large amount of circulating evidence, however, that in multiple cell types, e-liquids and e-cigarette vapours can lead to dysregulation of cellular behaviours leading to possible future disease and may have teratogenic effects. Future studies must therefore work to correlate human health effects with e-cigarette use, second/third-hand exposure and quit attempts.[20,21]

Smoking cessation

At present, the National Health Service (NHS) suggests that the best smoking cessation outcomes are achieved when a combination of specialist help, and smoking cessation medications are employed.[48] E-cigarettes have been marketed as an effective safe smoking cessation tool. However, many spurious claims regarding the efficacy in this regard have been made often by the very tobacco companies who produce them. Indeed, meta-analyses tackling this problem have often yielded varied results. This may in part be due to underlying trial method which often does not compare to standard NRTs or indeed no e-cigarette use as well as the variable definitions of smoking cessation among trials. In one systematic review that involved 18 observational studies and 2 RCTs which looked at the association between e-cigarette use and cessation in smokers including those wanting to quit, a pooled odds ratio of 0.63 (95% confidence interval (CI), 0.45–0.86) in achieving smoking cessation was calculated, highlighting their lack of efficacy.[11] However, a limitation to this review was the paucity of RCTs comparing e-cigarettes and other NRTs head-to-head. In the trial conducted by Bullen et al., one of the first RCTs, 657 participants were randomised to 16 mg nicotine e-cigarettes, 21 mg nicotine patches and placebo e-cigarettes (4:4:1) along with telephone/text support although this was only used in roughly 40% of all participants. Abstinence at 6 months was self-reported and correlated with eCO measurements and was 7.3%, 5.8% and 4.1%, respectively, which failed to show significance partly due to the high rate of loss to follow-up (22%). One of the few positive results was that participants using e-cigarettes showed a significant reduction in tobacco use at 6 months relative to nicotine patches but not e-cigarette placebo. Overall, this result seems to offer some basis for e-cigarette use possibly in the context of tailored support in reducing tobacco consumption.[19] In the Efficiency and Safety of an ECLAT trial that involved 300 current smokers with no intention to quit, participants were randomised between 7.2 mg/5.4 mg e-cigarettes and non-nicotine cigarettes; the results showed decreased cigarette consumption (confirmed by self-assessment and eCO measurement) and sustained abstinence but was once again limited by its small study size and not significant size effect.[12] Furthermore, a Cochrane systematic review suggested that the small number of RCTs and wide confidence intervals meant that no definitive conclusion could be made but did show that patients would likely reduce consumption when using e-cigarettes.[49]

These landmark trials while important were flawed by their use of current smokers with no intention to quit as well as their use of now obsolete e-cigarette devices which could not be depended on to provide consistent levels of nicotine and work for extended periods of time. As of this year, Hajek et al. reported the first randomised control trial of e-cigarettes versus NRT in motivated smokers attempting to quit and were not current users of either product. This UK-based trial involved 886 participants and ran for 52 weeks with weekly clinician meetings and carbon monoxide analysis at baseline 4 and 52 weeks. The NRT group used combinations of products while the e-cigarette group used a starter pack called One Kit with e-liquid containing nicotine (18 mg/mL). At 1 year, the abstinence rate was 17.7% in the e-cigarette group and 8% in the NRT group. Participants who did not achieve abstinence and used e-cigarettes showed a significant reduction in their eCO levels, suggesting decreased tobacco consumption. Interestingly, both interventions were less satisfying than tobacco cigarettes but neither resulted in serious side effects with the e-cigarette group that really showed an improvement in cough and phlegm production.[50] As such this article provides the first direct evidence that in motivated smokers with clinician support e-cigarettes can provide superior outcomes than traditional NRT, but these results need further corroboration. This idea of support in conjunction with e-cigarette use has shown promise; one study which looked at e-cigarette use as an additional tool in smoking cessation group therapy found that participants who used e-cigarettes versus other or no smoking cessation therapy were much less likely to be abstinent after 12 months follow-up. One reason cited for this is the lack of clear instruction on how e-cigarettes should be employed in patients with regard to the strength and quantity of e-cigarettes and the patient's background nicotine dependence and

duration of smoking. This does raise an important point for clinicians when possibly prescribing them for patients.[51] In a real-world setting, cross-sectional survey involving almost 6000 patients in the United Kingdom, it was found that patients who used e-cigarettes were 60% more likely to abstain than those using other forms of NRT or no aid at all when controlled for nicotine dependence. This study did, however, have significant flaws as abstinence relied on self-reporting and only 464 of the 6000 participants used e-cigarettes as their cessation tool.[52]

To assist healthcare practitioners in giving evidence-based instruction to patients regarding e-cigarette use and smoking cessation, there has been a push for more robust studies tackling their use. One multi-national study involving Australian, UK, Canadian and American smokers showed that, at 1-year follow-up, e-cigarette users are more likely to report decreased tobacco cigarette use, increased quit attempts but not necessarily increased abstinence.[8] Indeed, when enquiring in e-cigarette users the perceived efficacy of e-cigarettes, they showed that the anecdotal reports of success are often due to patients citing that vaping is pleasurable and identifiable to others as socially acceptable.[53] However, some groups remain less likely to respond to e-cigarette therapy, particularly cancer patients, who often have significant tobacco dependency; however, it is known that smoking can in the setting of cancer increase the risks of second primaries and result in treatment interruptions and increased symptom burden during the treatment period.[54] One study looking at 1074 cancer patients enrolled at a cancer centre over a 1-year period (2012–2013) reported during this time a threefold increase in e-cigarette use but reported that users were overall twice as likely to be smoking at follow-up with no evidence to support they assisted with cessation.[55]

This suggests that not only the type of patient but also the setting in which e-cigarettes are first employed and used may be important in their overall success. One recent hospital-based study looking at self-reported e-cigarette use was assessed at 1, 3 and 6 months post-discharge. It found that at 6 months, e-cigarette users were less likely to abstain from tobacco (risk difference, –16.5%), but this was heavily dependent on the pattern of e-cigarette use with regular use required to establish cessation.[56]

Finally, it is important to note that there is a growing concern that e-cigarettes could decelerate and even reverse the trend of decreasing societal tobacco smoking rates particularly in youths. This is based on the high prevalence and awareness of e-cigarette use within youths with up to 24% of American high school students having been exposed to e-cigarettes. In addition, the variety of flavours, social acceptability and sanctioned marketing as a cool alternative to tobacco products make e-cigarettes much more attractive to youths. Cross-sectional studies have shown that youths who engage in e-cigarette use are two to four times more likely to smoke tobacco-based cigarettes in later life, with one 2017 meta-analysis estimating that the pool OR of smoking initiation was 3.62 between ever versus never e-cigarette use.[19,57]

One 2019 cross-sectional survey studying this further in England, Scotland and Wales utilising national surveys used in secondary school patients found that since 1998 there had been positive changes in smoking attitudes over this period which seemed to be linked to e-cigarette awareness. In addition, it showed that the trend of ever smoking continued to decline although less than it had done so prior to e-cigarette introduction as it had done pre-1998. While this landmark study the first of its kind in the United Kingdom is important that we comment that with each year e-cigarettes come to resemble more traditional tobacco-cigarettes and achieve greater awareness and as such we could still see the resurgence of tobacco-based smoking.[58]

Conclusion

E-cigarettes are vigorously promoted by the tobacco industry, product manufacturers and trail outlets as new means to quit smoking and have consequently gained considerable public awareness. Currently, the greatest users of e-cigarettes are youths and current tobacco smokers. While many claims exist with regard to their efficacy, studies have yielded conflicting results but do highlight the role e-cigarettes may have in reducing smoking levels and helping promote smoking cessation with the first robust RCT providing encouraging results; however, further trials, systematic analysis and long-term follow-up are needed before this is certain. However, while their role continues to be defined, ongoing concerns exist with regard to their safety profile. Early in vitro and in vivo studies show they can upregulate pro-inflammatory cytokines in a plethora of cell types, increase susceptibility to infection and the development of emphysematous lesions in animals. This is not translated in the early human trials that have been conducted although larger more robust trials are needed before any definitive conclusion can be made. In addition, concerns have been raised to the effects they have in the unborn child with evidence that they may be linked with congenital deformities and structural changes within the foetal brain and lungs. Key safety issues remain their highly variable content of nicotine, carrier substances and flavouring chemicals as well as their unforeseen vaporisation products and the future risks of tobacco use. This narrative review while helpful in summarising what is known on this topic is limited by being narrative in nature and highlights the need for systematic review and meta-analysis. This would help to solidify what is known on this topic and minimise any reporting biases and incomplete retrieval of the literature. For clinicians, this review hopefully will alert them to engage in this discussion with patients while making them aware of potential links to ill health that remain unexplored and will require RCT and systematic analysis in the future.

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