

Smoking and age-related macular degeneration

Optometrist **Dr Rohit Narayan** reviews the impact of smoking on AMD, why it has such impact, and also whether e-cigarettes are safer for eye health

There is no doubt that age-related macular degeneration (AMD) has a multifactorial aetiology with a variety of risk factors. Several epidemiological studies across the world have demonstrated how smoking is a major modifiable risk factor. It is frequently associated with more severe forms of AMD,^{1,4} and increases the likelihood of both eyes being affected.⁵

DOES IT MATTER HOW LONG SOMEONE HAS SMOKED?

Smoking status and history is important and, although currently lacking a standardised definition, generally falls into three categories:

- Current smoker
- Previous smoker
- Never smoked

Several studies have compared different levels of smoking, classified as pack-years, and most of them confirmed a dose-response effect for AMD.⁴ Pack-years smoked better reflects the amount of exposure over a lifetime of smoking.⁶ To calculate pack-years of smoking, the average of the number of cigarettes smoked per day is divided by 20 to give packs per day and multiplied by the total number of years of smoking.^{7,8}

Current-smokers have two to four-fold increase in risk for developing AMD when compared to patients that never

smoked.⁹⁻¹¹ Current and former smokers were found to have an increased prevalence of late AMD, although a recent study also found an association of early AMD features with smoking.¹² The increased AMD risk appears to be higher in those patients who have smoked 20 pack-years and more.^{4,13} There is bad news for people living with smokers too: passive smoking, ie living with a smoker for five years or more, increases the risk for AMD among non-smokers.^{9,14}

WHY IS CIGARETTE SMOKE SO HARMFUL FOR THE RETINA?

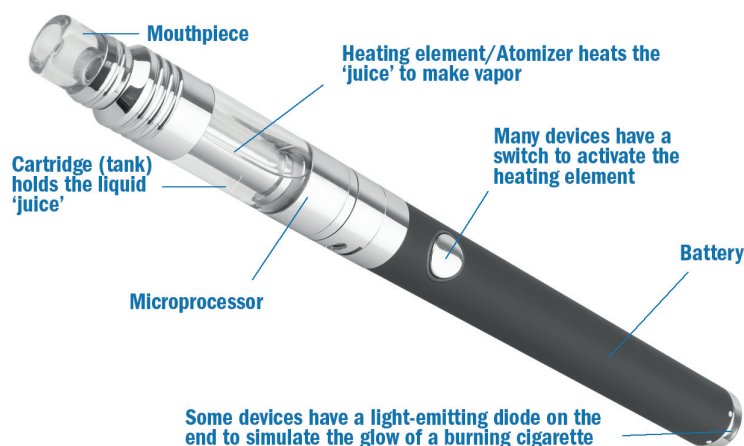
Cigarette smoke is comprised of a gas and tar phase containing over 4,700 chemicals, with a high concentration of free radicals.^{15,16} Gas-phase radicals include reactive oxygen species (ROS), epoxides, peroxides, nitric oxide (NO), nitrogen dioxide and various other free radicals. It has been estimated that each puff of a cigarette contains 1,015 free radicals, including superoxide anion and nitric oxide, that combine to form peroxynitrite, which is a potent oxidant that initiates lipid peroxidation.¹⁷

PATHOPHYSIOLOGY OF SMOKING

Cigarette smoke promotes molecular and pathological changes that may establish the ideal macular microenvironment for the development of AMD⁴ and has been linked to cellular changes in all retinal layers³ particularly the retinal pigment epithelium (RPE).^{4,18} These cellular changes involve a variety of mechanisms including vascular inflammation and endothelial dysregulation,^{4,19} oxidative damage,²⁰⁻²² toxic damage, and histopathological changes.^{4,23}

Cigarette smoke also induces 'pro-inflammatory' changes in the RPE through an important part of the immune system: increased expression of complement activation products with reduced expression of complement regulators.^{24,25} Cigarette smoke contains a large number of pro-oxidant compounds that increase oxidative stress, resulting in damage to the RPE and the alterations in the metabolic support of the RPE, ultimately causing apoptosis of the photoreceptors.²⁶ Oxidative stress is also thought to be pivotal in lipofuscin and drusen formation.^{4,27} Examples of pro-oxidant compounds in cigarette smoke include nicotine²⁸ and cadmium,²⁹ though the most abundant is hydroquinone which is commonly found in processed foods, plastic containers and atmospheric pollutants.^{30,31} Nicotine specifically has been found to cause vasoconstriction and is thought to impair choroidal blood flow.¹⁹ Hydroquinone is thought to be a key factor in the pathogenesis of dry AMD²² as well in the development of →

FIGURE 1 Components of an e-cigarette



CNV.³² Cigarette smoke can also cause toxic damage of the mitochondrial DNA within the RPE cell, contributing to the formation of drusen in individuals who are cigarette smokers.^{4,33,34}

Although the role of genetic testing is considered a research rather than a clinical tool at this moment, studies show a correlation between smoking and late AMD which appears greater in patients with certain higher risk genetic profiles, particularly linked to genes encoding for complement factor H (CFH) and age-related maculopathy susceptibility (ARMS),³⁵ and more recently in smokers with certain variants in nitric oxide synthase 2A (NOS2A).³⁶

E-CIGARETTES

A trend towards electronic cigarettes (ECs) is emerging as a potentially 'safer alternative' to conventional cigarettes. E-cigarettes were developed in China in the early 2000s and have gained in popularity.^{37,38} They are designed to deliver nicotine vapour without the toxic constituents of tobacco or tobacco combustion toxicants and carcinogens.³⁹

E-cigarettes have three components: the battery, the heating element or atomizer, and a cartridge or tank (figure 1). The tank holds a nicotine solution dissolved in propylene glycol, glycerol, or both, plus nicotine and a vast array of flavourant chemicals, ranging from fruit, chocolate, gummy bear, to nicotine and others (figure 2).⁴⁰ These elements are housed in a cylindrical container with some models looking very similar to traditional cigarettes, while others look like large pens with mouthpieces.

When an EC user takes a puff, the nicotine solution is heated and the vapor can be inhaled into lungs, where nicotine is rapidly delivered to the brain.^{38,41} ECs are tobacco products that deliver nicotine and so carry the risk of addiction⁴² and the potential to harm adolescent brain development.⁴⁰

Research regarding the benefits and risks of ECs are ongoing.⁴³ There has been much debate recently over whether ECs offer the possibility of reducing the harm (of lung cancer, cardiovascular disease and respiratory disease) for people who cannot, or will not, quit smoking conventional cigarettes, or whether they threaten the goal of further reducing tobacco smoking with particular impact on the young population. There appear to be two schools of thought; that of harm minimisation and that of a precautionary approach. Although there is some commonality, advocates on both sides have drawn conclusions that are often conflicting, creating a global divide on policy strategies.⁴⁴

Although ECs deliver lower levels of carcinogens than do conventional cigarettes, and therefore may pose less cancer risk to users (albeit not zero cancer risk),^{45,46,47} they still expose users to ultrafine particles and other toxins that may substantially increase cardiovascular^{48,49} and non-cancer lung disease risk^{50,51}.

There is conclusive evidence that in addition to Nicotine, most EC products contain and emit numerous potentially toxic substances,⁴² although it emits fewer toxicants than combustible tobacco products.

Research is currently lacking on the effect of nicotine and eye health and EC use specifically, although lab studies have provided a link with wet macular degeneration⁵² as well as risks of progression of wet AMD in passive smokers due to its effect on human retinal pigment epithelium (RPE).⁵³ The College of Optometrists has called for greater research into the ocular effects of ECs.⁵⁴

Public Health England (PHE) recently published a review of the evidence on ECs Feb 6, 2018.⁵⁵ ECs are not risk free and appropriate regulation is important. Policy on ECs in countries in the Organisation for Economic Co-operation and Development (OECD) is converging on a cautiously permissive approach.⁵⁶ The



FIGURE 2 E-cigarettes support a wide variety of flavours

conclusions of a previous PHE report 2015⁵⁷ were controversial (often cited as the '95% safe' debate) in providing qualified support for use of ECs, contributing to a shift in international opinion.⁵⁸

The PHE recent review of the evidence on ECs covers regulation, patterns of EC use, effectiveness of ECs in smoking cessation, and safety of ECs, nicotine, and novel heat-not-burn tobacco products.⁵⁵

Official guidance in the USA on ECs has been more precautionary, focusing on the potential risks, such as encouragement of youth smoking and the addictive nature of nicotine.⁵⁹

Of general concern is rapid increase in ECs among adolescents. In the US, adolescents using EC has risen 900% from 2011 to 2015, with e-cigarettes becoming the most commonly used form of tobacco among the youth.⁴⁰ Although ECs were designed to aid in smoking cessation, this is not the primary reason for use among youth and young adults.⁴⁰ It is suggested that EC usage among youth in the US leads to progression ('gateway' behaviour) to traditional cigarette smoking,^{42,60} however this is not the conclusion drawn by PHE (2018).⁵⁵

However, on core issues agreement is good between US⁵⁹ and UK⁶¹ official communications on ECs: both state that ECs can benefit smokers who are able to switch completely from smoked tobacco; neither recommend ECs for young people or non-smokers, supporting regulations to limit sales and decrease the appeal of e-cigarettes to adolescents and young adults; both agree ECs are not risk free and that more research is needed.

Specifically, the PHE's new review states that the evidence on ECs is incomplete but sufficient to guide current policy and continues to support the assumption of reduced risk of harm for ECs compared with smoking.⁵⁶ This has been echoed by the National Academies of Science and Engineering and Medicine (NASEM) recent review where the chair of the committee that wrote the report concluded 'E-cigarettes cannot be simply categorised as either beneficial or harmful. In some circumstances, such as their use by non-smoking adolescents and young adults, their adverse effects clearly warrant concern. In other cases, such as when adult smokers use them to quit smoking, they offer an opportunity to reduce smoking-related illness.'⁶²

In January this year, the US Annual Review of Public Health journal discussed evidence for a 'gateway' effect.⁶³ Research into e-cigarettes experimentation in the young transitioning into established smoking began in 2011,⁶⁴ with more recent studies as well as the US Surgeon General report (2016)⁴⁰ supporting the →



FIGURE 3 The IQOS device

gateway effect.^{60,65,66} Some researchers have stated e-cigarettes lead young people to cigarette use and nicotine addiction. Of concern, is that this pathway appears to be a 'one-way street', whereby e-cigarette products were not part of young people's efforts to quit.⁶⁷ It appears that lower-risk youth are being brought into the e-cigarette market, many of whom then transition to smoking cigarettes.⁶⁶ The 2015 US National Youth Tobacco Survey⁶⁸ confirms this process may be starting.

Substantial evidence reveals that flavouring encourages adolescent use,^{69,70,71} some citing 95% first e-cigarettes use by adolescents being flavoured compared to 44.1% of older adults⁷¹ Recent reviews in the UK (Public Health England) and in the USA (National Academies of Sciences and Engineering and Medicine (NASEM)) have supported more research into the potential risks from less well studied toxicants in many flavouring chemicals and device-specific metals.^{42,55}

The NASEM report concluded substantial evidence of e-cigarettes acting a gateway to smoking among the youth and young adults,⁴² the PHE report agreed that while young people who use ECs may go on to try smoking, this had no detectable effect on youth smoking rates and has not interrupted declining trends in youth smoking in many countries.⁵⁵

EC regulations have been revised recently. Falling into two categories, EC can be considered as a tobacco product and regulated under the newly revised Tobacco and Related Products Regulations 2016,⁷² with rules governing the manufacture, marketing and sale, or, as a medical product with licensing under the Medicines and Health Care products Regulation Agency (MHRA). Upon approval, successful applicants can license and market their product as a healthier alternative and effective at

helping smokers quit,⁷³ opening the possibility for prescribing under the NHS. An example being the MHRA's approval of British American Tobacco's (BAT) e-cigarette e-Voke (Nov 21, 2015),⁷⁴ although BAT recently decided (Feb 2018) not bring the product to market.⁷⁵

Studies have shown that adding ECs to tobacco smoking, or dual usage, did not facilitate smoking cessation or reduction. If e-cigarette safety is confirmed, the use of EC alone may facilitate smoking cessation.^{42,76,77,78} In terms of policy, all smokers should be supported to stop smoking completely, including those who smoke and use ECs. Support from smoking cessation clinics remains important in helping smokers to quit.⁶¹

There is at present little guidance offered by the Royal College of Ophthalmology or College of Optometrists⁷⁹ regarding e-cigarettes. Recent guidance from the Royal College of Physicians (2016) however, supports the use of EC as a mode of harm prevention in smokers.³⁹

More research is needed regarding EC. It is apparent that they are a growing part of the public health landscape and changing the way we view nicotine addiction. Health care providers should be more proactive in addressing nicotine and tobacco addiction with patients.⁴¹

THE '95% SAFER' DEBATE

Public Health England, an agency of the Department of Health, produced a report entitled, *E-cigarettes: an evidence update (2015)*⁸⁰ supported by many UK public health organisations (including Cancer Research, ASH, British Lung Foundation and Royal College of Physicians). The PHE report is built upon the idea that e-cigarettes may potentially represent a product that can reduce harm for established smokers. The report attracted international publicity^{39,44,80} stating that e-cigarettes are 95% less harmful than combustible cigarettes.

The '95% less harmful' claim originated from a consensus meeting of 12 people convened by Professor DJ Nutt in 2014.^{81,82} They reached this conclusion without citing any specific evidence.⁸³ The Nutt *et al* paper did include the caveat: 'A limitation of this study is the lack of hard evidence for the harms of most products on most of the criteria' (⁸² p. 224), which has generally been ignored by those quoting this report.^{84,85,86,87} Both the *Lancet* and the *British Medical Journal* questioned the PHE findings at the time.^{88,89}

The '95% safer' figure remains widely quoted, despite the fact that evidence of the potential dangers of e-cigarette use have accumulated since 2014. This new evidence indicates that the true risk of e-cigarette may be much higher than the '95% safer' claim would indicate.⁸¹

FIGURE 4 Apple store, left, and IQOS store, right



TABLE 1 Very Brief Advice (VBA – ‘Ask, Advise, Act’)

ASK	Establish and record smoking status (Pack years)	‘Do you (still) smoke? How many a day?’
ADVISE	How to stop	‘Obviously the choice is yours, but with the right support and treatment it’s easier to stop and stay stopped’
ACT	Offer help	‘There are all sorts of treatments along with support from someone trained to help people stop smoking can make a big difference. Would you be interested in that?’

WHAT’S THE FUTURE FOR SMOKING?

Heat-not-burn (HNB) tobacco products are the latest nicotine-containing innovation offered to smokers by the tobacco industry.⁹⁰ The most well-known device being the IQOS (I Quit Ordinary Smoking) by Philip Morris International (PMI).⁹¹ This sleek electronic device (figure 3) became available in England in December 2016⁹² being available from dedicated stores that look more like premium electronics outlets stores,⁹³ and some independent retailers (figure 4).

These devices consist of disposable tobacco sticks soaked in propylene glycol, which are inserted in a holder in the HNB cigarette. The tobacco is heated with an electric blade at 350°C (compared to 600°C to burn tobacco). The cigarettes are marketed by PMI as a ‘revolutionary technology that heats tobacco without burning it, giving you the true taste of tobacco, with no smoke, no ash and less smell’,⁹⁴ thereby producing less toxins overall than conventional cigarettes. There are currently few independent studies on heat not burn products. When levels of these toxins and carcinogens were measured independently, they appeared to be a lot higher than the manufacturer had claimed.^{91,95}

The FDA rejected the claim that PMI should be allowed to claim its iQOS electronic tobacco device can reduce the risk of tobacco-related diseases compared with traditional cigarettes.⁹⁶ PHE states the limited evidence on environmental emissions from use of these products suggests that harmful exposure from heated tobacco products is higher than from e-cigarettes, but further evidence is needed to be able to compare products.⁵⁵

WHAT CAN I DO AS AN EYE CARE PROFESSIONAL?

Smoking is a major risk factor and that is something that we should discuss with all patients. Given that smoking increases the risk of AMD at least two to four-fold,^{4,97} discussing its cessation is an important recommendation due to its potential to alter AMD progression.^{98,99}

As previously mentioned, ex-smokers still have an increased risk of developing AMD compared with never smokers,⁴ as does living with a smoker for at least five years.⁹ Perhaps rather alarmingly, studies have shown that the risk of late AMD remains present to some degree for up to 20 years after stopping smoking.^{4,13,100}

Recently, genetic testing has arisen as an option to provide patients with a certain risk profile based on high-risk genes for AMD.⁴ Such information might motivate patients to quit smoking.¹⁰¹⁻¹⁰⁴ At present, the majority of the peer-reviewed evidence suggests that genetic testing is more useful as a research tool than in Clinical management of patients although this may change in the future.¹⁰⁵ Even patients with neovascular AMD who smoke should be advised to quit, as their response to anti-VEGF intravitreal therapy is poorer than in non-smokers.¹⁰⁶

Public awareness of the link between smoking and ocular health is lacking.¹⁰⁷⁻¹⁰⁹ The role of eye care professionals is

therefore critical role in educating the public and encouraging smokers to quit.¹¹⁰ Awareness of the risk of blindness from smoking is low among teenagers, but fear of blindness may be more likely to motivate teenagers to stop smoking than fear of lung or heart disease.¹⁰⁸

A recent survey into patients perceptions and experience of an eye examination revealed they expected their eye care professional to examine their eye health, ask them about their smoking and diet habits, and indicated feeling comfortable discussing these topics with their primary eye care provider.¹¹¹ These findings suggest that brief momentary interventions relating to tobacco use and diet are likely to be acceptable to deliver in both ophthalmology and optometry settings.¹¹¹ As nicotine can be considered a drug, any discussions about tobacco use needs to begin with understanding that smoking is generally not a ‘bad habit’, but a physical addiction¹¹² with a high percentage (70%) of relapse.¹¹³ Most people who smoke require several ‘quit attempts’ before they are successful.^{114,115} Some studies quote patient compliance as low as 0%.¹¹⁶ In a 10 year study only one in four current smokers with any AMD at baseline quit smoking at five years and were still not smoking at 10 years; with 50% still smoking after 10 years.⁹⁷ Almost one third of adults smokers were either unaware or had difficulty understanding the effects of smoking on ocular health. It is therefore unlikely that any single health care provider or one single discussion will manage a patient’s addiction, and that patients will likely receive ongoing support from a range of providers including optometrists.¹¹² There is strong evidence that such advice and support can be effective in helping patients quit, and for many healthcare professional bodies, advice on smoking and cessation forms part of a duty of care.^{117,118}

Time constraints and a perceived need for further training in this area^{4,119} may be why there is no consistent approach among clinicians in documenting patients’ smoking history or advising on smoking cessation.^{110,111,120}

The College of Optometrists has raised smoking awareness through its *Lifestyles and eyes*, *Cataracts* and *Macular degeneration* leaflets. This, coupled with guidelines for other primary care providers, can be adapted into an optometric setting.¹¹² Some focus on connecting a patient with a specific cessation support service, while other approaches rely on the provider to personally support patient cessation.¹¹² Studies in UK optometric settings have demonstrated the feasibility of delivering brief smoking cessations with good success¹²² and optometrists and trainees¹²³ should be encouraged to find out what cessation supports are available in their community.¹¹²

A variety of training programmes exist for all levels of healthcare professionals (see below). Of particular interest to optometrists is the National Centre for Smoking Cessation and Training (NCSCCT) which offers a ‘Very Brief Advice’ module aimed at clinicians who provide smoking cessation and support as a small part of their wider role.¹²⁴ These web-based programmes include video simulations of discussing smoking and →


PEARLS

- Smoking is a major modifiable risk factor associated with AMD
- Smoking increases the risk of AMD two-four fold.
- Pack-years smoked better reflects the amount of exposure.
- Cigarette smoke is comprised of a gas and tar phase containing chemicals with a high concentration of free radicals
- Cigarette smoke induces 'pro-inflammatory' changes in the RPE, along with oxidative damage.
- Risk of AMD remains present up to 20 years after cessation of smoking.
- Passive smoking carries risk of AMD.
- Public awareness of the link between smoking and ocular health is lacking.
- Eye care providers have a duty of care to inform patients of the long-term ocular risk of smoking and AMD.
- Electronic cigarettes are considered 'safer' than conventional cigarettes, although more research is needed.
- Smoking cessation (using VBA) with a discussion of dietary modification is recommended.
- AREDS and AREDS II formulations only indicated in intermediate/late stage AMD.
- AREDS formula (beta carotene) carries increased risk of lung cancer in smokers.
- AREDS II: lutein+zeaxanthin a better substitute for beta carotene.

its cessation in a variety of patient scenarios. See table 1.

Stopping smoking is tough. Smokers know they should stop, yet often they do not know how, or that support is available. There are many factors influencing a patient's ability to quit, and although offering VBA can be influential, it may not result in a quit attempt at that time, however that should not prevent the clinician presenting it at subsequent visits.¹²⁴

With the proper training and resources, it is certain that the optometric community can and will play a greater role in addressing tobacco-use cessation among patients. Many community pharmacists are knowledgeable and can offer advice over the counter. Strategies such as VBA, used as part of our everyday routine, can influence a patient's potential success in quitting.^{112,124}

In a case of smoking history alone, smoking cessation with a discussion of toward the possible benefit(s) of dietary modification, including natural consumption of the xanthophyll pigments has been advocated.^{125,126} AREDS formulations are only appropriate in intermediate or late AMD stage.¹²⁷ If considering an AREDS based approach in a smoker, one must balance the possible risks with the benefits of the intervention.¹²⁸ Smokers who fit the AREDS criteria should be cautioned against consumption of the original AREDS formulation containing high-dose beta-carotene supplementation, because of the potential increased risk of lung cancer in current smokers and former smokers.¹²⁹⁻¹³¹ More recently, The AREDS2 Study suggested that lutein and zeaxanthin could be a safe alternative carotenoid substitute in the AREDS formulation.¹³² 

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USEFUL WEBSITES

- Local stop smoking service (NHS): <https://www.nhs.uk/smokefree>
- Information on treatment options: <https://www.nhs.uk/conditions/stop-smoking-treatments/asp>
- www.ncsct.co.uk
- www.makingeverycontactcount.co.uk

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