Is nicotine damaging to oral tissues?

BDJ Team is pleased to be sharing content from sister publication *Evidence-Based Dentistry (EBD)*. *EBD* delivers the best available evidence on the latest developments in oral health. In this summary review, **Deborah Moore**¹ provides a commentary on *Effect of nicotine on human gingival, periodontal ligament and oral epithelial cells. A systematic review of the literature.* (*J Dent* 2019; **86**: 81-88) written by Holliday R S, Campbell J and Preshaw P M.

Practice points

- Patients can be advised that nicotine is not the harmful component of smoking
- Smoking cessation which includes nicotine replacement is much more successful than behavioural approaches alone
- Dental practitioners are well-placed to address widespread misconceptions about nicotine replacement therapy.

Abstract

Data sources The review included 42 pre-clinical *in-vitro* studies, published between 1995 and 2017.

Study selection The study selected *in-vitro* studies which had assessed the effect of nicotine on human gingival and periodontal fibroblasts and epithelial cells. Typically, diluted pure nicotine was added to a cell culture medium in a variety of doses for a variety of time periods and the cells were then compared against a no-nicotine control. Outcomes assessed were: Cell viability, cell attachment

or adhesion, cell proliferation or inflammatory mediator production. Studies were restricted to English language and full-text only.

Data extraction and synthesis Two members of the review team screened abstracts and reviewed the full-texts independently. Disagreements regarding inclusion were resolved by discussion and consultation with the third author. Data were also extracted independently using a specifically designed data extraction form which included a quality assessment specifically designed for *in-vitro* studies. A narrative synthesis of the results was carried out.

Results The included studies were heterogeneous in their designs, with a wide variety of cell types, concentrations of nicotine (1 nM to 100 mM), exposure times (30 minutes to four weeks), and assays used. All studies were assessed at being at high risk of bias due to lack of randomisation, allocation concealment, and blinding. No effect on cell viability was observed when the nicotine concentrations used

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were within the ranges observed *in-vivo* in smokers, nicotine replacement therapy users (NRT) and e-cigarette users. Cell viability was adversely affected only when concentrations of nicotine reached those observed in the saliva of smokeless tobacco users (>5 mM). However, periodontal ligament cells are not usually exposed to saliva *in-vivo*. Effects on cell attachment, cell proliferation and production of inflammatory mediators were reported at a wide range of concentrations, but the effects were contradictory. The authors make several recommendations for future research in this area, to improve the quality of the primary studies.

Conclusions At the concentrations found in smokers and users of NRT including e-cigarettes, nicotine is unlikely to be toxic to human gingival and periodontal ligament cells in *in-vitro*. Higher concentrations of nicotine, of the levels observed in the saliva of smokeless tobacco users, have been shown to be cytotoxic *in-vitro*.

Commentary

It is difficult to overstate the harmful effects of smoking: two out of three smokers who start at a young age will be killed by it, losing on average ten years of life.¹ Aside from the life-threatening consequences, including oral and pharyngeal cancer, we know that smoking increases the risk of periodontal disease by 85%.² The emergence of nicotine replacement therapies (NRT) over the last 40 years has dramatically increased the success rate of smokers who want to quit. In a Cochrane overview of systematic reviews, Cahill *et al.* demonstrated that 80% more people quit when using NRT compared to placebo.³ To date, the only serious adverse event that has emerged during the long history of NRT is an excess of heart palpitations, though this is very rare, occurring in 2.5% of participants using NRT compared to 1.5% of those in placebo groups.³ Despite this strong record of safety and effectiveness, only half of UK smokers think that NRT is any less harmful than smoking, with misperceptions greater in more disadvantaged groups.⁴

Public misperceptions may have worsened recently due to controversy surrounding a particular type of NRT: e-cigarettes.⁵ At the time of writing, 18 deaths in the US have been attributed to e-cigarette use and several hundred cases of respiratory illness have been reported.⁶ The specific chemical that is causing the lung injury is unknown at present, but the US CDC reports that the majority of cases have involved illicit e-cigarettes that contain tetrahydrocannabinol (THC), the psychoactive component of marijuana that

produces the 'high'.⁶ Whilst these reports are alarming, it must be remembered that there are significant differences between the US and the UK in terms of e-cigarette policy. In the UK, e-cigarettes are promoted as a harm-reduction strategy for smoking cessation, and are subject to some of the tightest regulatory controls in the world. They cannot be sold to under-18s, cannot be advertised, and they must adhere to minimum standards for safety and quality, which are enforced by the Medicines and Healthcare products Regulatory Agency (MHRA). The MHRA also run a yellow-card reporting system for adverse effects and safety concerns.⁷

The most common reason for using e-cigarettes in the UK is to stop smoking, with use amongst never-smokers very rare, less than 1%. In the US, e-cigarettes are promoted through social media and traditional advertising channels, which has resulted in a dramatic rise in their use amongst young people. This has not been observed in the UK, where just 1.7% of 11-18-year-olds reported at least weekly use in 2018. Furthermore, the maximum permitted concentration of nicotine in e-cigarettes in the UK is 20 mg/mL, which is much lower than the 59 mg/mL found in some US e-cigarettes.⁴ A recent randomised controlled trial carried out in NHS stop smoking services found that when combined with face-to-face behavioural support, e-cigarettes were twice as effective for smoking cessation at 1-year than traditional NRT such as gum or patches.⁸ The most recent evidence review by Public Health England (PHE) recommends that whilst vaping is not without risk, it should be described to patients and the public as 'at least 95% less harmful than smoking'.⁴ To further reduce the prevalence of smoking, widespread misconceptions about nicotine replacement therapy, including e-cigarettes, need to be addressed.⁴

This study is a well-conducted systematic review which provides further evidence that nicotine is not the harmful component of cigarette smoking. Dental teams are encouraged to continue to recommend smoking cessation services and nicotine replacement therapies to their patients, following the 'Very Brief Advice' model.^{9,10} Brief interventions in a dental setting have been shown to increase quit rates amongst smokers.¹¹ It is worth remembering that if you have helped two smokers quit, you have saved at least one life.¹²

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