An update on e-cigarettes and orthodontics

Short Title: Vaping and Orthodontics

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<u>Abstract</u>

E-cigarettes can be a useful cessation aid for adult smokers. However, use of e-cigarettes by young people in the UK has been on the rise and is of increasing concern. The implications of e-cigarette use amongst patients undergoing orthodontic treatment has not yet been reviewed. This narrative review explores the emerging evidence base underpinning the relationship of e-cigarette use on tooth movement, demineralisation, and surgical outcomes.

Single sentence relevance statement

The usage of e-cigarettes has rapidly increased, and it is important to understand the possible implications for orthodontic treatment.

Single sentence objective statement

To inform the reader of the current evidence base surrounding e-cigarette use and specifically the relationship with orthodontic treatment.

Introduction

Many health behaviours have the potential to impact on orthodontic treatment for example, dietary factors, oral hygiene habits and tobacco smoking. Electronic cigarettes (e-cigarettes) have been available now for over 15 years in the UK, with specific EU regulation since 2014. ^[1] It is estimated that 4.5 million UK adults currently use e-cigarettes ^[2] and they have been the most popular quit aid used by smokers since 2013. ^[3] There is high-certainty evidence that e-cigarettes are effective for smoking cessation and have increased quit rates compared to conventional nicotine replacement therapy. ^[4,5]

Youth use of e-cigarettes had remained relatively low and stable until 2022 when a sudden increase was seen. Regular usage (more than once a week) in 11-17 year old has increased from 1.2% in 2021 to 3.7% in 2023 (Figure 1). ^[6] Eighteen percent of 18-year-olds were current e-cigarette users in 2023 (Action on Smoking and Health, ASH). This increase has largely been put down to the use of disposable products (Figure 2 and Figure 3). ^[6] There has been public health concern about this increase and a government consultation and proposed regulation to ban disposable products and increase flavour and packaging restrictions.

There is wide consensus that e-cigarette use is significantly less harmful than smoking, but not risk free. For smokers using e-cigarettes as a quit aid, any potential risks from e-cigarette use are likely greatly outweighed by stopping tobacco smoking. However, for a young person who is a non-smoker, e-cigarettes will pose health impacts. Additionally young people may be particularly prone to effects given their continued development and the delicate nature of some tissues. ^[7]

Several previous papers and resources have explored the potential oral health effects of ecigarette use. ^[8,9] This paper will focus specifically on the potential orthodontic implications of e-cigarette use. This may help guide future research and inform clinical practice.

Orthodontic specific aspects of interest

E-cigarette use may impact the following areas that are particularly relevant for an orthodontic patient: tooth movement, caries, surgical healing, and staining. The following sections will review and summarise the evidence base across these areas.

Orthodontic tooth movement

Orthodontic tooth movement (OTM) is a dynamic process dependent on active bone remodeling described by the pressure-tension theory. ^[10] This complex process is regulated by several key factors, including osteoprotegerin, prostaglandins, and cytokines. Importantly, force-induced aseptic inflammation plays a pivotal role in OTM and requires strict control to prevent side effects, which can include alveolar bone loss, root resorption, and destruction of periodontal tissues. ^[11]

No studies have directly evaluated the impacts of e-cigarette use on tooth movement in either clinical or laboratory studies. However, studies have investigated the relationship of nicotine alone on OTM in animal models (rats and mice). Interestingly several studies found that nicotine was associated with accelerated rates of tooth movement all finding the most significant differences between the highest strength nicotine group and the control group (no nicotine). ^[12,13, 14] Sodagar et al (2011) increased the nicotine dose and identified an increase in mean amounts of tooth movement from 0.4mm, 0.62mm and 0.78mm compared to 0.21mm in the control group. One study found nicotine exposure significantly increased orthodontically Induced Inflammatory Root Resorption (OIIRR) ^[14] and another looked histologically and reported 'unbalanced resorption-apposition bone remodelling patterns and increased osteoclast cell distribution'. ^[15] Another study found conflicting results, reporting no significant impact of nicotine on tooth movement. ^[16] The authors of this study discuss limitations of the previous studies (showing accelerated tooth movement) including measurement methods and nicotine administration timing.

These studies all used daily subcutaneous injections of nicotine. A single bolus of high dose nicotine is unlikely to be comparable to the daily nicotine profile seen in either tobacco smokers or e-cigarette users. Hence, there are limitations in how much can be extrapolated from these studies to clinical scenarios. Nevertheless, the animal studies reveal insights into the potential effects of nicotine exposure from e-cigarettes on OTM. Further research, ideally on humans, is required to fully understand the effects on human oral physiology.

Caries and Demineralisation

Patients undergoing orthodontic treatment with fixed appliances are at an increased risk of developing caries and white spot lesions. One meta-analysis reported an incidence of new carious lesions during orthodontic treatment as 45.8% with a prevalence of 68.4%. ^[17] It should be noted that caries and decalcification occurrence can vary depending on individual risk factors and the impact of socio-economic status and area deprivation cannot be underestimated. ^[18] Multiple studies have demonstrated an increase in plaque accumulation associated with fixed orthodontic appliances, however, are limited by fairly small sample sizes. ^[19,20,21] With recent data suggesting that the proportion of young people experimenting with vaping has grown by 50% year on year, it is important to consider the association between e-cigarettes, caries and erosion among this cohort of patients. ^[6]

An association has been suggested between e-cigarette use and caries. The strongest evidence to date comes from a cross-sectional study of self-reported data. Individuals who used e-cigarettes were more likely to have untreated caries (odds ratio, 1.69; 95% CI, 1.24 to 2.29) than those who had never smoked or used e-cigarettes. ^[22] However, as discussed by the study authors, because of the cross-sectional design, causality could not be established. Also, although they controlled for some demographic factors, they were not able to adjust for some important factors such as diet.

Much of the available data is therefore limited to in vitro studies. It has been suggested that e-cigarette aerosols promote a significantly higher adhesive force between the enamel surface and *S. mutans*, a facultatively anaerobic bacterium implicated within the dental caries process. The e-liquids used in this study were produced by the research group, rather than using products available on the market. ^[23] Separate laboratory-based studies highlighted enhanced biofilm formation and attachment of *S. mutans but* suppressed the growth of early colonisers *S. sanguinis* and *S. gordonii*. ^[24, 25] Given that all the aforementioned bacteria are implicated in the ecological plaque hypothesis, the findings are contradictory as to the impact on caries development.

Saliva has an important protective effect on the oral cavity. Individuals suffering from reduced quality or quantity of saliva suffer from increased caries and tooth surface loss rates. ^[26] A common reported side effects of e-cigarette use is oral dryness which could be related to the hygroscopic nature of several of the carrier agents in the e-liquids (propylene glycol and vegetable glycerine). ^[27] This could be a potential mechanism for an increased caries rate.

When considering the erosive potential, an analysis of 45 e-cigarette liquids (e-liquids) available online in the UK found that several products had a pH below 5.5, with the authors concluding potential erosive effects. ^[28] Caution must be drawn from this laboratory-based study which does not account for the buffering effect of saliva, the complexities of the oral microbiome nor the titratability of the acid. How readily acids disassociate is of more consequence than a low pH in isolation. Most importantly, it should be noted that the study only highlighted the erosive potential of products that did not contain nicotine. The nicotine containing samples (which are more representative of the products used by the general population) had an alkaline pH.

In summary, the body of evidence indicates a noteworthy association between e-cigarette use and an increased risk of caries. However, these findings are not without limitations including methodological constraints and the reliance on self-reported data. Further research is essential to determine the extent of the relationship between e-cigarette use and caries and erosion risk with special consideration for those undergoing orthodontic treatment.

E-cigarettes and surgery

Traditional tobacco smoking is a well-established risk factor for adverse outcomes following surgery, including increased surgical site infections. ^[28] Similarly, orthognathic surgery patients who smoke are more likely to experience these infections. ^[29] Many harmful components of tobacco smoke, such as carbon monoxide and hydrogen cyanide, are likely to be responsible for these negative effects. E-cigarettes, on the other hand, either lack these components entirely or contain them at significantly lower levels. Therefore, it is

hypothesised that e-cigarette use may be associated with fewer adverse postoperative outcomes compared to tobacco smoking.

As with other areas explored in this review, there is a paucity of direct clinical evidence on the impact of e-cigarettes on surgical outcomes. Existing research is primarily limited to case reports; animal and human studies using surrogate physiologic markers for cutaneous wound healing and cell line laboratory studies. ^[30,31] These studies raise concerns about potential negative effects of e-cigarettes on inflammation, oxidative stress, endothelial dysfunction, blood flow/oxygenation, and platelet function.

The vasoactive and wound healing effects of nicotine are complex and warrant further investigation. Traditionally nicotine is considered a vasoconstrictor due to its sympathomimetic properties. ^[32] However, a recent study has questioned the role of nicotine in this process, although still reporting a similar vasoconstrictive effect of e-cigarette use. ^[33] Conversely, other studies suggest nicotine may reduce inflammation, ^[34] accelerate wound healing (in diabetic mice), and promote wound angiogenesis ^[35,36] The potential benefits of topical nicotine application for wound healing were even explored by oral and maxillofacial surgeons through a series of publications ^[37], including a small pilot clinical trial with 10 participants. This found a statistically significant, initial increase in buccal mucosa tissue perfusion amongst e-cigarette users with nicotine compared to without. ^[38] Some clinical studies have shown an association between e-cigarette use and gingival bleeding. ^[39] However, interpreting these findings is challenging as users often quit tobacco smoking concurrently, which is known to increase gingival bleeding, making it difficult to isolate the specific impact of e-cigarette use. ^[39,40] Further clinical research is necessary to determine the precise role of nicotine in wound healing.

Given the high volume of surgeries performed worldwide and the widespread use of ecigarettes for over a decade, the lack of robust clinical studies reporting adverse surgical outcomes in this population is surprising and perhaps telling in its own right – if there were major impacts of e-cigarette use on surgical outcomes, we would perhaps expect to see a strong signal of this in the evidence base. For elective procedures like orthognathic surgery, where the consequences of complications are high, it remains prudent to minimise all modifiable risk factors. Ideally, patients should abstain from both smoking and vaping before undergoing surgery.

Staining

Tobacco smoking is well known to cause staining of the dental hard tissues. ^[41] In the context of orthodontics this has relevance to restorative materials, in particular resin composites. A recent, comprehensive systematic review examined the evidence for staining caused by novel nicotine products, including e-cigarettes. The review found low-quality evidence suggesting that e-cigarettes may cause staining, but to a lesser degree than cigarette smoke. ^[40]

Discussion

We have reviewed the evidence for adverse oral health impacts of e-cigarette use across four clinical areas of relevance to orthodontics. There are several common themes across the areas: the evidence base is generally weaker quality and not conclusive, the indication is that the oral health effects are relatively minimal but further research is needed. In our opinion, possible increased caries risk is one of the areas with the strongest data to date and one to watch as the evidence develops.

Cigarette smoking is not an absolute contraindication for orthodontic treatment but carries increased risks and patients should be provided with evidence-based cessation interventions. ^[42, 43] E-cigarettes are the most common quit aid being used by smokers (in England) ^[44] and are recommended by the NHS and NICE as options smokers can consider. ^[45, 46] Robust evidence shows e-cigarettes are more effective than conventional treatments such as nicotine replacement therapy. ^[4] Hence, adult orthodontic patients who are current or former smokers, may be using e-cigarettes as part of a current or recent quit attempt. The advice for dual users (i.e., those smoking and vaping) is that they should quit smoking completely. For vapers, the current NHS advice is that they should aim to quit vaping as well but not to rush this process and only do it when they are sure they will not go back to smoking. ^[46]

Given the typical young patient population in orthodontics and current trends in tobacco cigarette and e-cigarette use, a common scenario we face clinically is a young person who has never smoked but who is using an e-cigarette. In this situation, we should engage in a non-judgmental conversation with the patient, presenting the current uncertainties surrounding e-cigarettes' oral health impacts based on available research. While e-cigarette use is not an absolute contraindication for orthodontic treatment, in the author's opinion, it likely carries a slightly increased risk of complications, particularly when considering surgical options. There are a range of concerns for young people using e-cigarettes: unnecessary addiction (disruption to education), unnecessary costs, environmental impact, and general health impacts such as lung damage or causing harm to the developing brain. ^[47, 48] For a young person seeking orthodontic treatment, the interaction with an orthodontist could be a powerful motivator to quit vaping.

Conclusion

Tobacco smoking is a well-documented risk factor for various adverse oral health outcomes. Emerging evidence suggests that e-cigarette use might also have detrimental effects on oral health during orthodontic treatment, although likely to a lesser extent than tobacco smoking. However, the current evidence in this area is limited and of weak quality. Further well-designed studies are crucial to definitively understand the impact of e-cigarettes on oral health in orthodontic patients. This is particularly important for young people who may have never smoked tobacco before but use e-cigarettes. In the interim, it is advisable for healthcare professionals to encourage and support orthodontic patients, especially young people, to reduce or ideally eliminate their e-cigarette use altogether.

Figure legends



ASH Smokefree GB Youth Surveys. 2014-2023. Unweighted base: All 11-17 year olds (2013=1,895, 2014=1,817, 2015=1,834, 2016=1,735, 2017=2,151, 2018=1,807, 2019 =1,982, 2020 =2,029, 2021=2,109, 2022=2,111, 2023=2,028)

Figure 1: Regular usage (more than once a week) in 11-17 year old has increased from 1.2% in 2021 to 3.7% in 2023 (ASH)



Figure 2: Disposable e-cigarette products.



ASH Smokefree GB Youth Surveys. Unweighted base: 11-17 year olds who are current users of e-cigarettes (2015 = 41, 2016=36, 2017=60, 2018=59, 2019=94, 2020=94, 2021=76, 2022=172, 2023=187)

Figure 3: Most frequently used e-cigarette by device type, current GB youth (11-17) users of e-cigarettes, 2015-2023.

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References:

- The Tobacco and Related Products Regulation 2016. Available at <u>https://www.legislation.gov.uk/uksi/2016/507/contents/made</u>. (Accessed May 2024)
- Office for National Statistics. Adult smoking habits in the UK: 2022. Available at: <u>https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlif</u> <u>eexpectancies/bulletins/adultsmokinghabitsingreatbritain/2022</u> (Accessed May 2024).
- Smoking in England. Discover Major Findings Relating to Smoking in England. Available at: <u>Monthly Tracking KPI - Graphs - Smoking in England</u>. (Accessed May 2024).
- 4. Hartmann-Boyce J, Lindson N, Butler AR, McRobbie H, Bullen C, Begh R, et al. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 2022; 11: CD010216.
- British Society of Periodontology and Implant Dentistry. Is vaping harmful to oral health? Available at: <u>Is vaping harmful to oral health?</u> | <u>BSP (bsperio.org.uk)</u>. (accessed May 2024).
- Action on smoking and health. Use of e-cigarettes among young people in Great Britain. Available at: <u>https://ash.org.uk/resources/view/use-of-e-cigarettes-among-young-people-in-great-britain</u> (Accessed May 2024).
- Holliday R, Chaffee BW, Jakubovics NS, Kist R, Preshaw PM. Electronic Cigarettes and Oral Health. J Dent Res 2021; 100: 906-913.
- 8. Taylor G, McNeill A, Girling A, Farley A, Lindson-Hawley N, Aveyard P. Change in mental health after smoking cessation: systematic review and meta-analysis. Bmj. 2014 Feb 13;348.
- 9. Chaffee BW, Couch ET, Vora MV, Holliday R. Oral and periodontal implications of tobacco and nicotine products. Periodontol 2000. 2021; 87: 241-253.
- 10. Wise GE, King GJ. Mechanisms of tooth eruption and movement. J Dent Res. 2008; 87: 414-434.
- 11. Li Y, Jacox LA, Little SH, Ko CC. Orthodontic tooth movement: The biology and clinical implications. Kaohsiung J Med Sci. 2018; 34: 207-214.
- Bakathir MA, Linjawi AI, Omar Samia S, Aboqura AB, Hassan AH. Effects of nicotine on bone during orthodontic tooth movement in male rats. Histological and immunohistochemical study. Saudi Med J 2016; 37: 1127-1135.
- 13. Sodagar A, Donyavi Z, Arab S, Kharrazifard MJ. Effect of nicotine on orthodontic tooth movement in rats. Am J Orthod Dentofacial Orthop. 2011; 139: e261-265.
- 14. Kirschneck C, Bauer M, Gubernator J, Proff P, Schroder. Comparative assessment of mouse models for experimental orthodontic tooth movement. Sci Rep. 2020; 10: 12154.
- 15. Bakathir MA, Linjawi AI, Omar SS, Aboqura AB, Hassan AH. Effect of nicotine on bone during orthodontic tooth movement in male rats. Saudi Med J 2016; 37: 1127-1135.

- Araujo CM, Rocha AC, Araujo BM, Johann ACBR, Pereira LF, Tanaka OM et al. Effect of acute administration of nicotine and ethanol on tooth movement in rats. Braz Oral Res. 2018; 11:32:e96.
- Sundararaj D, Venkatachalapathy S, Tandon A, Pereira A. Critical evaluation of incidence and prevelance of white spot lesions during fixed orthodontic appliance treatment: A metaanalysis. J Int. Soc Prev Community Dent. 2015; 5: 433-439.
- Inequalities in oral health in England 2021.
 https://www.gov.uk/government/publications/inequalities-in-oral-health-in-england
 (Accessed May 2024).
- Naranjo AA, Trivino ML, Jaramillo A, Betancourth M, Botero JE. Changes in the subgingival microbiota and periodontal parameters before and 3 months after bracket placement. Am J Orthod Dentofacial Orthop. 2006; 130: 275.e17-e22.
- 20. Klukowska M, Bader A, Erbe C, Bellamy P, White DJ, Anastasia MK et al. Plaque levels of patients with fixed orthodontic appliances measured by digital plaque analysis. Am J Orthod Dentofacial Orthop. 2011; 139: e463-e470.
- 21. Shokeen B, Viloria E, Duong E, Rizvi M, Murillo G, Mullen J et al. The impact of fixed orthodontic appliances and clear aligners on the oral microbiome and the association with clinical parameters. Am J Orthod Dentofacial Orthop. 2022; 161: e475-e485.
- Vemulapalli A, Mandapati SR, Kotha A, Aryal S. Association between vaping and untreated caries: A cross-sectional study of National Health and Nutrition Examination Survey 2017-2018 data. J Am Dent Assoc. 2021; 152: 720-729.
- 23. Kim SA, Smith S, Beauchamp C, Song Y, Chiang M, Giuseppetti A et al. Cariogenic potential of sweet flavors in electronic-cigarette liquids. PLoS One. 2018; 13:e0203717.
- Rouabhia M, Semlali A. Electronic cigarette vapor increases Streptococcus mutans growth, adhesion, biofilm formation, and expression of the biofilm-associated genes. Oral Dis. 2021; 27: 639-647.
- 25. Catala-Valentin A, Bernard JN, Caldwell M, Maxson J, Moore SD, Andl CD. E-Cigarette Aerosol Exposure Favors the Growth and Colonization of Oral Streptococcus mutans Compared to Commensal Streptococci. Microbiol Spectr 2022; 10: e02421.
- Guo X, Hou L, Peng X, Tang F. The prevalence of xerostomia among e-cigarette or combustible tobacco users: A systematic review and meta-analysis. Tob Induc Dis. 2023; 9: 21-22.
- 27. Fairchild R, Setarehnejad A. Erosive potential of commonly available vapes: a cause for concern? Br Dent J. 2021; 231: 487-491.

- 28. Sorensen LT. Wound healing and infection in surgery. The clinical impact of smoking and smoking cessation: a systematic review and meta-analysis. Arch Surg. 2012; 147: 373-383.
- 29. Kuhlefelt M, Laine P, Suominen AL, Lindqvist C, Thorén H. Smoking as a significant risk factor for infections after orthognathic surgery. J Oral Maxillofac Surg. 2012 ;70:1643-1647.
- Ashour O, Al-Huneidy L, Noordeen H. The implications of vaping on surgical wound healing: A systematic review. Surgery. 2023;173:1452-1462.
- 31. Thieman T, Westmark D, Sutton A. Electronic cigarettes and cutaneous wound healing: A systematic review. J Am Acad Dermatol. 2023; 88:911-912.
- 32. Whitehead AK, Erwin AP, Yue X. Nicotine and vascular dysfunction. Acta Physiol (Oxf). 2021; 231: e13631.
- Pitzer CR, Aboaziza EA, O'Reilly JM, Mandler WK, Olfert IM. Nicotine and Microvascular Responses in Skeletal Muscle from Acute Exposure to Cigarettes and Vaping. Int J Mol Sci. 2023; 24:10208.
- Misery L. Nicotine effects on skin: are they positive or negative? Exp Dermatol. 2004; 13: 665-70.
- Jacobi J, Jang JJ, Sundram U, Dayoub H, Fajardo LF, Cooke JP. Nicotine accelerates angiogenesis and wound healing in genetically diabetic mice. Am J Pathol. 2002; 161: 97-104.
- 36. Martin JW, Mousa SS, Shaker O, Mousa SA. The multiple faces of nicotine and its implications in tissue and wound repair. Exp Dermatol. 2009; 18: 497-505.
- 37. Reuther WJ, Brennan PA. Is nicotine still the bad guy? Summary of the effects of smoking on patients with head and neck cancer in the postoperative period and the uses of nicotine replacement therapy in these patients. Br J Oral Maxillofac Surg. 2014 Feb; 52:102-105.
- 38. Reuther WJ, Hale B, Matharu J, Blythe JN, Brennan PA. Do you mind if I vape? Immediate effects of electronic cigarettes on perfusion in buccal mucosal tissue--a pilot study. Br J Oral Maxillofac Surg. 2016; 54: 338-341.
- 39. Silveira ML, Everard CD, Sharma E, Lauten K, Alexandridis AA, Duffy K et al. Tobacco Use and Incidence of Adverse Oral Health Outcomes Among US Adults in the Population Assessment of Tobacco and Health Study. JAMA Netw Open. 2022; 5: e2245909.
- 40. Wadia R, Booth V, Yap HF, Moyes DL. A pilot study of the gingival response when smokers switch from smoking to vaping. Br Dent J. 2016; 221: 722-726.
- Karanjkar RR, Preshaw PM, Ellis JS, Holliday R. Effect of tobacco and nicotine in causing staining of dental hard tissues and dental materials: A systematic review and meta-analysis. Clin Exp Dent Res. 2023; 9:150-164.

- 42. Holliday R, Hong B, McColl E, Livingstone-Banks J, Preshaw PM. Interventions for tobacco cessation delivered by dental professionals. Cochrane Database Syst Rev. 2021; 2: CD005084.
- Delivering better oral health: an evidence-based toolkit for prevention. Available at: <u>https://www.gov.uk/government/publications/delivering-better-oral-health-an-evidence-based-toolkit-for-prevention</u> (Accessed May 2024).
- Vaping in England: evidence update February 2021. Available at: <u>https://www.gov.uk/government/publications/vaping-in-england-evidence-update-february-2021</u> (Accessed Ma 2024).
- 45. National Institute for Health and Care Excellence. Tobacco: preventing update, promoting quitting and treating dependence. NICE guideline [NG 209]. Available at: <u>Recommendations</u> on treating tobacco dependence | Tobacco: preventing uptake, promoting quitting and <u>treating dependence | Guidance | NICE</u> (Accessed May 2024).
- 46. NHS Live Well. Using e-cigarettes to stop smoking. Available at: <u>Using e-cigarettes to stop</u> <u>smoking - NHS (www.nhs.uk)</u> (Accessed May 2024).
- 47. Banks E, Yazidjoglou A, Brown S, Nguyen M, Martin M, Beckwith K et al. Electronic cigarettes and health outcomes: umbrella and systematic review of the global evidence. Med J Aust. 2023; 218: 267-275.
- Dwyer JB, McQuown SC, Leslie FM. The dynamic effects of nicotine on the developing brain.
 Pharmacol Ther. 2009; 122: 125-139.