What every dentist needs to know about electronic cigarettes

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Electronic cigarette (EC) use is on a steady rise, leading to increased concerns about its efficacy with regard to tobacco cessation goals and safety with regard to systemic and oral health. Recent studies have shown that EC flavoring agents can have adverse effects similar to those of combustible tobacco products. Evidence is mounting that EC use should not be considered a healthier alternative to tobacco smoking. The aerosols produced by ECs have been associated with respiratory, cardiac, and central nervous system disease as well as oral mucosal alterations. In addition, ECs can affect kidney and liver function. Their use has also resulted in EC explosions and burn injuries, some of which have been fatal. The aim of this article is to review the systemic and oral health concerns associated with EC use.

Received: April 2, 2020
Accepted: August 26, 2020

Keywords: electronic cigarettes, oral, review, systemic

GENERAL DENTISTRY SELF-INSTRUCTION CE CREDIT
Exercise No. GD475, p. 36
Subject code: Tobacco Cessation (158)

To reduce the adverse health effects of tobacco and maintain the satisfaction of smoking, an electronic nicotine delivery system was developed in 2003.[1] This product, commonly referred to as an *electronic cigarette* (EC), has also been promoted as a smoking cessation device.[1] ECs consist of a rechargeable battery, a cartridge containing a fluid ("e-liquid"), and an atomizer that warms and aerosolizes the e-liquid.[2] The e-liquid component is available with a multitude of flavoring agents that can be purchased in combination with various nicotine concentrations or without nicotine. Additionally, ethanol, tetrahydrocannabinol (THC) extracts, and other psychoactive drugs can be inserted into the e-liquid for recreational use.[3]

There are several designs on the market, including tanks and "mods" (tube- or box-shaped ECs), which are rechargeable or disposable. Some ECs look similar to regular cigarettes, cigars, or pipes, while others resemble pens, USB storage devices, and other everyday items.[4] In 2017, 2.8% of US adults were current EC users, with sales totaling approximately $10 billion.[4,5] There is a rise in EC use among former tobacco smokers, current smokers, and nonsmokers.[5] The use of ECs by teenagers increased from 1.5% in 2011 to 20.8% in 2018, surpassing conventional cigarette use.[6] In 2019, 5 million middle and high school students reported using ECs in the past 30 days, with greater prevalence in the lesbian, gay, bisexual, and transgender community and in children of lower socioeconomic status.[7,8]

The popularity of ECs can be attributed to their marketable appeal as a healthier alternative to combustible tobacco and a smoking cessation tool. There is an incorrect perception among users that ECs lower the risk of oral and lung cancer as well as respiratory and cardiovascular diseases caused by conventional cigarette smoking.[9,10] In fact, the efficacy with regard to tobacco cessation goals and safety of EC are widely debated. There is no evidence that ECs are a healthier option than combustible tobacco. In fact, they are considered less effective in helping patients successfully quit smoking and have been linked with the abuse of other substances such as alcohol and marijuana.[11,12]

The purpose of this article is to review the emerging evidence of the oral and systemic sequelae and the risk of physical injuries associated with EC use.

Systemic health concerns

Although the effects of tobacco smoking on oral and systemic health are well described in the literature, additional research is needed to clarify the systemic health risks of ECs. The increased worldwide use of ECs necessitates examination of their biologic effects on different parts of the body. There are many brands, each with a diversity of flavors and inherent chemical characteristics, making it difficult to analyze toxicity using standardized methods. However, recent studies have suggested that EC use alone or in conjunction with combustible tobacco

is an independent risk factor for respiratory, cardiovascular, and central nervous system disorders and can impair kidney and liver function. These findings will be reviewed in the following sections.

Respiratory system

In 2019, the US Centers for Disease Control and Prevention (CDC) reported the emergence of 2300 cases of e-cigarette or vaping product use–associated lung injury (EVALI).[13] The majority of patients were described as critically ill, and there were 47 confirmed fatalities.[13] Most of the patients were younger than 35 years, and 14% were under the age of 18 years.[13] As of August 2019, 215 cases were documented in 25 US states, including the death of an adult from Illinois.[14] Examples of the pulmonary diseases associated with EVALI are chemical pneumonitis, acute eosinophilic pneumonia, acute and subacute hypersensitivity pneumonitis, lipoid pneumonia, metal fume fever, acute lung injury, and organizing pneumonia.[15]

Several components of ECs have been linked to respiratory system impairment, principally propylene glycol and vegetable glycerin, which increase mucin expression and reduce membrane fluidity in airway epithelia.[16] Diacetyl, commonly used as a flavoring agent in e-liquids, is well known for causing bronchitis obliterans and pulmonary toxicity.[17,18] According to the CDC, vitamin E acetate, a compound used in the fabrication of EC-related products that contain THC extract, was detected in 29 patients with EVALI.[19] For this reason, the CDC has labeled vitamin E acetate a "chemical of concern" and strongly recommends that it should be excluded from ECs and related products.[19]

Vaporized e-liquid contents contain other toxic chemicals that, when inhaled, cause proinflammatory and immunosuppressive changes in the respiratory mucosa independent of nicotine.[20] The thermal degraded products of propyl and glycol and vegetable glycerin (formaldehyde, acetaldehyde, and acrolein) have been detected in high concentrations in the majority of EC vapors analyzed.[21] These compounds have been implicated as carcinogens that can cause lung cell damage (via free radical release) and lung tissue inflammation when inhaled.[22] ECs can also induce oxidative stress (OS) and promote DNA fragmentation in human lung fibroblast and epithelial cells.[23,24]

Nicotine is packaged in varying concentrations for EC use. Nicotine can affect any organ where nicotinic acetylcholine receptors (nAChRs) are expressed, alter inflammation in the airway, and lead to dysregulated repair that can modify susceptibility to infection.[25] Acute exposure to nicotine-containing ECs can lead to airway remodeling and generate airway conditions that mimic the pathogenesis of chronic obstructive pulmonary pathosis, such as airway hyperactivity, distal airspace enlargement, excess mucin production, and increased cytokine and protease expression.[25-27]

Preliminary data have shown that smokers (conventional or EC users) infected with SARS-CoV-2 were 1.4 times more likely than nonsmokers to exhibit more severe pulmonary manifestations of COVID-19 and nearly 2.4 times more likely to need admission to the intensive care unit, require mechanical ventilation, or die.[28] Similarly, smokers experienced more severe respiratory disease in earlier MERS-CoV outbreaks.[29,30]

Cardiovascular system

The effects of long-term use of tobacco cigarettes on the cardiovascular system are well reported. Analogously, several studies have found evidence that use of ECs can promote pathophysiologic changes in the heart.[31] Yan and D'Ruiz demonstrated that EC use elevates heart rate and diastolic blood pressure in smokers but to a lesser extent than combustible cigarettes.[32] The vapor from ECs has also promoted platelet aggregation in healthy people.[33] A single use of an EC increases markers of OS (NOX2-derived peptide and 8-iso-prostaglandin $F_{2\alpha}$), decreases nitrous oxide bioavailability, and decreases flow-mediated dilation (an established marker of endothelial dysfunction in humans) at a level similar to tobacco cigarettes.[34] Therefore, inhaling 10 puffs of EC vapor (equivalent to smoking a cigarette) is associated with an increase in endothelial progenitor cells and vascular changes.[35] The nicotine concentration in EC smokers is sufficiently elevated to maintain dependence on the addictive substance, with the result that adolescents often shift to tobacco smoking into adulthood.[36]

Animal studies have also shown that exposure to formaldehyde can decrease heart rate and blood pressure.[37-40] Formaldehyde has also been linked to OS and heart cell damage.[41] Acrolein, a ubiquitous aldehyde contaminant, is implicated in myocardial dysfunction and dilated cardiomyopathy in mice.[42] Although the detected levels of these aldehydes are low in ECs, secondhand exposure can still pose health concerns, especially in individuals with cardiovascular disease, children, and pregnant women.[43]

Central nervous system

There is evidence of increased levels of psychological distress, including a higher incidence of depression, mania, alcohol and illicit substance abuse, and suicidal ideation, among EC users compared to nonusers.[44-46] Many of the compounds found in EC vapors can trigger OS at levels similar to those of traditional cigarettes.[34] The developing brain is vulnerable to damage from smoke-induced OS, provoking alterations in the DNA repair system and contributing to the pathogenesis of psychiatric and neurodegenerative disorders.[47,48] Elevated levels of OS disrupt the development of the cerebral cortex and hippocampus, resulting in memory impairment and cognitive decline.[49,50]

Furthermore, elevated levels of OS have been associated with explosive disorder (abrupt episodes of violent behavior or angry verbal outburst) and aggression.[51] Use of ECs has also been linked with increased impulsivity and adolescent delinquency.[52-54] Moreover, exposure to EC vapor during periods of rapid brain growth was found to cause persistent behavioral changes and hyperactivity in an animal study.[55] Taken together, these findings suggest that ECs can play a role in attention deficits, impaired memory, poor learning and academic performance, increased aggressive and impulsive behavior, and increased depression and suicidal ideation in adolescents.[56]

Renal system

Tobacco smoking accelerates the progression of chronic kidney disease.[57] Nicotine in tobacco induces the production of reactive oxygen species and is responsible for renal injury due to OS and altered antioxidant response.[58] The nephrotoxic potential of ECs has yet to be determined. Whether e-liquids can induce renal OS at levels similar to conventional cigarettes has yet to be

corroborated. Nevertheless, Golli et al studied the impact of EC exposure on rat kidney and found that ECs can alter antioxidant defense and promote minor changes in renal function, such as blood urea, uric acid, and creatine levels.[59]

Hepatic system

Studies in mice have found that intraperitoneal nicotine injections in combination with a high-fat diet resulted in OS.[60,61] Hasan et al also demonstrated that e-liquid that contains nicotine could trigger OS, activate hepatocyte apoptosis, and result in hepatic steatosis in a mouse model of nonalcoholic fatty liver disease.[61] While there is no conclusive evidence linking EC use with liver disease, Espinoza-Derout et al reported that EC exposure increased OS in hepatic cell lines, leading to DNA damage and possible mitochondrial dysfunction.[62] The health implications of these findings are not yet clearly understood.

Oral health concerns

Epidemiologic studies have shown a positive correlation between combustible tobacco products and increased risks of periodontitis, oral cancer, tooth loss, and dental implant failures.[63] Despite the sudden rise in recreational use of ECs in the past decade, their effects on the oral cavity are not as well established. However, studies have shown that EC users are more susceptible to gingivitis, bone loss, and tooth fracture than nonsmokers.[64-67] Exposure to EC aerosols can also contribute to the pathogenesis of periodontitis via inflammatory cytokine release from periodontal fibroblasts and gingival epithelial progenitor cells.[68]

Aldehydes such as acrolein and formaldehyde can cause OS and carbonyl stress, leading to impaired wound healing in the periodontium.[69] The interaction of nicotine with EC flavoring agents has also been correlated with impaired periodontal wound healing due to disruption with oral myofibroblast differentiation and consequent reduction in myofibroblast contraction.[70] The use of ECs can also lead to bone loss, inflammation, and higher plaque index and probing depths with dental implants.[71,72] In vivo studies have shown that the interaction of EC flavoring agents with nicotine have resulted in increased cytotoxicity and apoptosis of gingival fibroblasts.[73,74]

It is important to note that aerosols from flavored e-liquids have similar rates of cariogenicity to high-sucrose, gelatinous candy and acidic beverages.[75] Nicotine in e-liquids facilitates an increased adhesion of *Streptococcus mutans,* doubling the production of oral biofilms and increasing the potential for dental caries.[75] Another common adverse effect of EC use is xerostomia and an attendant increased risk for caries, attributed to propylene glycol and glycerol and their increased promotion of water absorption.[76] There is also evidence that chronic EC consumers have a greater prevalence of oral mucosal lesions such as nicotine stomatitis, hairy tongue, and angular cheilitis than do former cigarette smokers.[77]

The e-liquids in ECs contain a variety of carcinogens, and preliminary studies have raised concerns about their potential cancer risk. EC-exposed cell lines have demonstrated significantly reduced cell viability and increased rates of apoptosis and necrosis, regardless of e-liquid nicotine content.[78] EC vapor, both with nicotine and without, is cytotoxic to epithelial cell lines and is a DNA strand break-inducing agent.[78] The amount of nicotine in some ECs approaches levels comparable to tobacco cigarettes, and in vitro studies indicate that nicotine can induce apoptosis and dysplastic changes in keratinocytes and induce oral precancerous lesions.[79-81] Investigations of the long-term use of ECs are needed to establish whether it results in any increased risk of malignancy in the oral cavity or other sites, particularly the lungs.

Electronic cigarette explosions

From 2015 to 2017, hospital emergency departments in the United States recorded 2035 EC-related explosions and burn injuries.[82] These hazards have been attributed to the creation of a "thermal runaway" effect (an exothermic reaction that results from rapid temperature increases that can potentially lead to an explosion) when the self-contained lithium-ion batteries of ECs are exposed to moisture or create a short circuit with other metallic objects.[83-89] The majority of reported EC-related injuries have been severe and include tooth fractures and avulsions, jaw fracture, ocular injuries, thermal burns to the oral mucosa and face, and coma. To date, at least 2 fatalities have been attributed to EC explosions. The first death involved a 38-year-old man who received a projectile wound to the head and experienced burns on about 80% of his body.[90,91] The second death occurred when an exploding EC severed the user's carotid artery, causing cerebral infarction and herniation.[92]

Conclusion

Growing laboratory and clinical evidence has demonstrated that the use of ECs can promote an array of systemic and oral disorders. Dental practitioners should remain vigilant for oral mucosal disease and dental caries susceptibility among their patients who use these devices and discuss with them the potential health concerns regarding these products.

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Disclaimer

The authors report no conflicts of interest pertaining to any of the topics discussed in this article.

References

1. Sultan AS, Jessri, M, Farah CS. Electronic nicotine delivery systems: oral health implications and oral cancer risk. *J Oral Pathol Med.* 2021;50(3):316-322.
2. Bozier J, Chivers EK, Chapman DG, et al. The evolving landscape of e-cigarettes: a systematic review of recent evidence. *Chest.* 2020;157(5):1362-1390.
3. Audrain-McGovern J, Stone MD, Barrington-Trimis J, Unger JB, Leventhal AM. Adolescent e-cigarette, hookah, and conventional cigarette use and subsequent marijuana use. *Pediatrics*. 2018;142(3):e20173616. doi:10.1542/peds.2017-3616
4. Brooks JK, Kleinman JW, Brooks JB, Reynolds MA. Electronic cigarette explosion associated with extensive intraoral injuries. Dent Traumatol. 2017;33(2):149-152.
5. Wang TW, Asman K, Gentzke AS, et al. Tobacco product use among adults - United States, 2017. *MMWR Morb Mortal Wkly Rep.* 2018;67(44):1225-1232.
6. Park E, Livingston JA, Wang W, Kwon M, Eiden RD, Chang YP. Adolescent e-cigarette use trajectories and subsequent alcohol and marijuana use. *Addict Behav.* 2020;103:106213. doi:10.1016/j.addbeh.2019.106213
7. Cullen KA, Gentzke AS, Sawdey MD, et al. e-Cigarette use among youth in the United States, 2019. *JAMA.* 2019;322(21):2095-2103.
8. Worku D, Worku E. A narrative review evaluating the safety and efficacy of e-cigarettes as a newly marketed smoking cessation tool. *SAGE Open Med.* 2019;7:2050312119871405. doi:10.1177/2050312119871405

9. Roditis M, Delucchi K, Cash D, Halpern-Felsher B. Adolescents' perceptions of health risks, social risks, and benefits differ across tobacco products. *J Adolesc Health.* 2016;58(5):558-566.
10. Chaffee BW, Gansky SA, Halpern-Felsher B, Couch ET, Essex G, Walsh MM. Conditional risk assessment of adolescents' electronic cigarette perceptions. *Am J Health Behav*. 2015;39 (3):421-432.
11. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *Lancet Respir Med.* 2016;4(2):116-128.
12. Roditis ML, Halpern-Felsher B. Adolescents' perceptions of risks and benefits of conventional cigarettes, e-cigarettes, and marijuana: a qualitative analysis. *J Adolesc Health.* 2015;57(2): 179-185.
13. Stanbrook MB. Vaping-associated lung illnesses highlight risks to all users of electronic cigarettes. *CMAJ*. 2019;191(48):E1319-E1320.
14. Centers for Disease Control and Prevention. Statement from CDC Director Robert R. Redfield, M.D., and Acting FDA Commissioner Ned Sharpless, M.D., on federal and state collaboration to investigate respiratory illness reported after use of e-cigarette products. *CDC Newsroom.* August 30, 2019. Accessed April 2, 2020. https://www.cdc.gov/media/releases/2019/s0830-statement-e-cigarette.html
15. Ansari-Gilani K, Petraszko AM, Teba CV, et al. E-cigarette use related lung disease, review of clinical and imaging findings in 3 cases. *Heart Lung*. 2020;49(2):139-143.
16. Gotts JE, Jordt SE, McConnell R, Tarran R. What are the respiratory effects of e-cigarettes? *BMJ*. 2019;366:l5275. doi:10.1136/bmj.l5275
17. Holden VK, Hines SE. Update on flavoring-induced lung disease. *Curr Opin Pulm Med*. 2016; 22(2):158-164.
18. Allen JG, Flanigan SS, LeBlanc M. et al. Flavoring chemicals in e-cigarettes: diacetyl, 2,3-pentanedione, and acetoin in a sample of 51 products, including fruit-, candy-, and cocktail-flavored e-cigarettes. *Environ Health Perspect*. 2016;124(6):733-739.
19. Lal A, Mishra AK, Sahu KK. Vitamin E acetate and e-cigarette or vaping product-associated lung injury (EVALI): an update. *Am J Med.* 2020;133(5):e204. doi:10.1016/j.amjmed.2019.11.005
20. Tomar SL, Hecht SS, Jaspers I, Gregory RL, Stepanov I. Oral health effects of combusted and smokeless tobacco products. *Adv Dent Res*. 2019;30(1):4-10.
21. Klager S, Vallarino J, MacNaughton P, Christiani DC, Lu Q, Allen JG. Flavoring chemicals and aldehydes in e-cigarette emissions. *Environ Sci Technol*. 2017;51(18):10806-10813.
22. Ratajczak A, Feleszko W, Smith DM, Goniewicz M. How close are we to definitively identifying the respiratory health effects of e-cigarettes? *Expert Rev Respir Med*. 2018;12(7):549-556.
23. Lerner CA, Rutagarama P, Ahmad T, Sundar IK, Elder A, Rahman I. Electronic cigarette aerosols and copper nanoparticles induce mitochondrial stress and promote DNA fragmentation in lung fibroblasts. *Biochem Biophys Res Commun.* 2016;477(4):620-625.
24. Gerloff J, Sundar IK, Freter R, et al. Inflammatory response and barrier dysfunction by different e-cigarette flavoring chemicals identified by gas chromatography–mass spectrometry in e-liquids and e-vapors on human lung epithelial cells and fibroblasts. *Appl In Vitro Toxicol*. 2017;3(1):28-40.
25. Wang Q, Khan NA, Muthumalage T, et al. Dysregulated repair and inflammatory responses by e-cigarette-derived inhaled nicotine and humectant propylene glycol in a sex-dependent manner in mouse lung. *FASEB Bioadv.* 2019;1(10):609-623.
26. Garcia-Arcos I, Geraghty P, Baumlin N, et al. Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. *Thorax*. 2016;71(12):1119-1129.
27. Ghosh A, Coakley RC, Mascenik T, et al. Chronic e-cigarette exposure alters the human bronchial epithelial proteome. *Am J Respir Crit Care Med.* 2018;198(1):67-76.
28. Vardavas CI, Nikitara K. Covid-19 and smoking: a systematic review of the evidence. *Tob Induc Dis*. 2020;18:20. doi:10.18332/tid/119324
29. Park JE, Jung S, Kim, Park JE. MERS transmission and risk factors: a systematic review. *BMC Public Health*. 2018;18(1):574. doi:10.1186/s12889-018-5484-8
30. Arcavi L, Benowitz NL. Cigarette smoking and infection. *Arch Intern Med*. 2004;164(20):2206-2216.
31. MacDonald A, Middlekauff HR. Electronic cigarettes and cardiovascular health: what do we know so far? *Vasc Health Risk Manag*. 2019;15:159-174. doi:10.2147/VHRM.S175970
32. Yan X, D'Ruiz C. Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. *Regul Toxicol Pharmacol.* 2015;71(1):24-34.
33. Hom S, Chen L, Wang T, Ghebrehiwet B, Yin W, Rubenstein DA. Platelet activation, adhesion, inflammation, and aggregation potential are altered in the presence of electronic cigarette extracts of variable nicotine concentrations. *Platelets.* 2016;27(7):694-702.
34. Carnevale R, Sciarretta S, Violi F, et al. Acute impact of tobacco vs electronic cigarette smoking on oxidative stress and vascular function. *Chest*. 2016;150(3):606-612.
35. Antoniewicz L, Bosson JA, Kuhl J, et al. Electronic cigarettes increase endothelial progenitor cells in the blood of healthy volunteers. *Atherosclerosis*. 2016;255:179-185.
36. US Department of Health and Human Services. *E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General*. US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2016. Accessed March 15, 2021. https://e-cigarettes.surgeongeneral.gov/documents/2016_SGR_Full_Report_non-508.pdf
37. Tani T, Kogi K, Horiguchi Y. Inhibitory effects of formaldehyde inhalation on the cardiovascular and respiratory systems in unanesthetized rabbits. *Jpn J Pharmacol.* 1986;40(4):551-559.
38. Tani T, Satoh S, Horiguchi Y. The vasodilator action of formaldehyde in dogs. *Toxicol Appl Pharmacol*. 1978;43(3):493-499.
39. Egle JL Jr. Effects of inhaled acetaldehyde and propionaldehyde on blood pressure and heart rate. *Toxicol Appl Pharmacol.* 1972;23(1):131-135.
40. James TN, Bear ES. Cardiac effects of some simple aliphatic aldehydes. *J Pharmacol Exp Ther.* 1968;163(2):300-308.
41. Güleç M, Songur A, Sahin S, Ozen OA, Sarsilmaz M, Akyol O. Antioxidant enzyme activities and lipid peroxidation products in heart tissue of subacute and subchronic formaldehyde-exposed rats: a preliminary study. *Toxicol Ind Health*. 2006;22(3):117-124.
42. Ismahil MA, Hamid T, Haberzettl P, et al. Chronic oral exposure to the aldehyde pollutant acrolein induces dilated cardiomyopathy. *Am J Physiol Heart Circ Physiol*. 2011;301(5):H2050-H2060.
43. Qasim H, Karim ZA, Rivera JO, Khasawneh FT, Alshbool FZ. Impact of electronic cigarettes on the cardiovascular system. *J Am Heart Assoc.* 2017;6(9):e006353. doi:10.1161/JAHA.117.006353
44. Chadi N, Li G, Cerda N, Weitzman ER. Depressive symptoms and suicidality in adolescents using e-cigarettes and marijuana: a secondary data analysis from the youth risk behavior survey. *J Addict Med*. 2019;13(5):362-365.
45. Jaycox LH, Stein BD, Paddock S, et al. Impact of teen depression on academic, social, and physical functioning. *Pediatrics*. 2009;124(4):e596-e605. doi:10.1542/peds.2008-3348
46. Leventhal AM, Strong DR, Sussman S, et al. Psychiatric comorbidity in adolescent electronic and conventional cigarette use. *J Psychiatr Res*. 2016;73:71-78.
47. Ikonomidou C, Kaindl AM. Neuronal death and oxidative stress in the developing brain. *Antioxid Redox Signal.* 2011;14(8):1535-1550.
48. Song P, Zou MH. Roles of reactive oxygen species in physiology and pathology. In: Wang H, Patterson C, eds. *Atherosclerosis: Risks, Mechanisms, and Therapies.* Wiley; 2015:379-392.
49. Hritcu L, Ciobica A, Gorgan L. Nicotine-induced memory impairment by increasing brain oxidative stress. *Cent Eur J Biol.* 2009;4(3):335-342.
50. Collins N, Sachs-Ericsson N, Preacher KJ, Sheffield KM, Markides K. Smoking increases risk for cognitive decline among community-dwelling older Mexican Americans. *Am J Geriatr Psychiatry.* 2009;17(11):934-942.
51. Coccaro EF, Lee R, Gozal D. Elevated plasma oxidative stress markers in individuals with intermittent explosive disorder and correlation with aggression in humans. *Biol Psychiatry.* 2016;79(2):127-135.
52. Chivers LL, Hand DJ, Priest JS, Higgins ST. E-cigarette use among women of reproductive age: impulsivity, cigarette smoking status, and other risk factors. *Prev Med.* 2016;92:126-134.
53. Grant JE, Lust K, Fridberg DJ, King AC, Chamberlain SR. E-cigarette use (vaping) is associated with illicit drug use, mental health problems, and impulsivity in university students. *Ann Clin Psychiatry.* 2019;31(1):27-35.
54. Jackson DB, Boccio CM, Leal WE, Vaughn MG. It's all the rage! Exploring the nuances in the link between vaping and adolescent delinquency. *J Crim Justice.* 2019;63:58-69.
55. Smith D, Aherrera A, Lopez A, et al. Adult behavior in male mice exposed to e-cigarette nicotine vapors during late prenatal and early postnatal life. *PLoS One*. 2015;10(9):e0137953. doi:10.1371/journal.pone.0137953
56. Tobore TO. On the potential harmful effects of e-cigarettes (EC) on the developing brain: the relationship between vaping-induced oxidative stress and adolescent/young adults social maladjustment. *J Adolesc.* 2019;76:202-209.
57. Orth SR, Ritz E, Schrier RW. The renal risks of smoking. *Kidney Int.* 1997;51(6):1669-1677.
58. Muthukumaran S, Sudheer AR, Menon VP, Nalini N. Protective effect of quercetin on nicotine-induced prooxidant and antioxidant imbalance and DNA damage in Wistar rats. *Toxicology.* 2008;243(1-2):207-215.
59. Golli NE, Jrad-Lamine A, Neffati H, et al. Impact of e-cigarette refill liquid exposure on rat kidney. *Regul Toxicol Pharmacol.* 2016;77:109-116.
60. Friedman TC, Sinha-Hikim I, Parveen M, et al. Additive effects of nicotine and high-fat diet on hepatic steatosis in male mice. *Endocrinology.* 2012;153(12):5809-5820.
61. Hasan MK, Friedman TC, Sims C, et al. α-7-Nicotinic acetylcholine receptor agonist ameliorates nicotine plus high-fat diet-induced hepatic steatosis in male mice by inhibiting oxidative stress and stimulating AMPK signaling. *Endocrinology.* 2018;159(2):931-944. Erratum: 2018;159(3):1416.
62. Espinoza-Derout J, Shao XM, Bankole E, et al. Hepatic DNA damage induced by electronic cigarette exposure is associated with the modulation of NAD+/PARP1/SIRT1 axis. *Front Endocrinol (Lausanne).* 2019;10:320. doi:10.3389/fendo.2019.00320
63. Jiang X, Jiang X, Wang Y, Huang R. Correlation between tobacco smoking and dental caries: a systematic review and meta-analysis. *Tob Induc Dis.* 2019;17:34. doi:10.18332/tid/106117
64. Akinkugbe AA. Cigarettes, e-cigarettes, and adolescents' oral health: findings from the population assessment of tobacco and health (PATH) study. *JDR Clin Trans Res.* 2019;4(3):276-283.
65. Atuegwu NC, Perez MF, Oncken C, Thacker S, Mead EL, Mortensen EM. Association between regular electronic nicotine product use and self-reported periodontal disease status:

population assessment of tobacco and health survey. *Int J Environ Res Public Health*. 2019;16(7):1263. doi:10.3390/ijerph16071263
66. Vora MV, Chaffee BW. Tobacco-use patterns and self-reported oral health outcomes: a cross-sectional assessment of the population assessment of tobacco and health study, 2013-2014. *J Am Dent Assoc.* 2019;150(5):332-344.e2. doi:10.1016/j.adaj.2018.12.004
67. Cho JH. The association between electronic-cigarette use and self-reported oral symptoms including cracked or broken teeth and tongue and/or inside-cheek pain among adolescents: a cross-sectional study. *PloS One.* 2017;12(7):e0180506. doi:10.1371/journal.pone.0180506
68. Ralho A, Coelho A, Ribeiro M, et al. Effects of electronic cigarettes on oral cavity: a systematic review. *J Evid Based Dent Pract*. 2019;19(4):101318. doi:10.1016/j.jebdp.2019.04.002
69. Sundar IK, Javed F, Romanos GE, Rahman I. E-cigarettes and flavorings induce inflammatory and pro-senescence responses in oral epithelial cells and periodontal fibroblasts. *Oncotarget.* 2016;7(47):77196-77204. doi:10.18632/oncotarget.12857
70. Lei W, Lerner C, Sundar IK, Rahman I. Myofibroblast differentiation and its functional properties are inhibited by nicotine and e-cigarette via mitochondrial OXPHOS complex III. *Sci Rep.* 2017;7:43213. doi:10.1038/srep43213
71. Al-Aali KA, Alrabiah M, ArRejaie AS, Abduljabbar T, Vohra F, Akram Z. Peri-implant parameters, tumor necrosis factor-alpha, and interleukin-1 beta levels in vaping individuals. *Clin Implant Dent Relat Res*. 2018;20(3):410-415.
72. AlQahtani MA, Alayad AS, Alshihri A, Correa FO, Akram Z. Clinical peri-implant parameters and inflammatory cytokine profile among smokers of cigarette, e-cigarette, and waterpipe. *Clin Implant Dent Relat Res.* 2018;20(6):1016-1021.
73. Sancilio S, Gallorini M, Cataldi A, di Giacomo V. Cytotoxicity and apoptosis induction by e-cigarette fluids in human gingival fibroblasts. *Clin Oral Investig.* 2016;20(3):477-483.
74. Willershausen I, Wolf T, Weyer V, Sader R, Ghanaati S, Willershausen B. Influence of e-smoking liquids on human periodontal ligament fibroblasts. *Head Face Med.* 2014;10:39. doi:10.1186/1746-160X-10-39
75. Kim SA, Smith S, Beauchamp C, et al. Cariogenic potential of sweet flavors in electronic-cigarette liquids. *PLoS One*. 2018;13(9):e0203717. doi:10.1371/journal.pone.0203717
76. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. *Int J Environ Res Public Health*. 2014;11(4):4356-4373.
77. Bardellini E, Amadori F, Conti G, Majorana A. Oral mucosal lesions in electronic cigarettes consumers versus former smokers. *Acta Odontol Scand.* 2018;76(3):226-228.
78. Yu V, Rahimy M, Korrapati A, et al. Electronic cigarettes induce DNA strand breaks and cell death independently of nicotine in cell lines. *Oral Oncol*. 2016;52:58-65.
79. Etter JF. Levels of saliva cotinine in electronic cigarette users. *Addiction*. 2014;109(5):825-829.
80. Wang C, Niu W, Chen H, et al. Nicotine suppresses apoptosis by regulating α7nAChR/Prx1 axis in oral precancerous lesions. *Oncotarget*. 2017;8(43):75065-75075. doi: 0.18632/oncotarget.20506
81. Wisniewski DJ, Ma T, Schneider A. Nicotine induces oral dysplastic keratinocyte migration via fatty acid synthase–dependent epidermal growth factor receptor activation. *Exp Cell Res.* 2018;370(2):343-352.
82. Rossheim ME, Livingston MD, Soule EK, Zeraye HA, Thombs DL. Electronic cigarette explosion and burn injuries, US emergency departments 2015–2017. *Tob Control.* 2019;28(4):472-474.
83. Rogér JM, Abayon M, Elad S, Kolokythas A. Oral trauma and tooth avulsion following explosion of e-cigarette. *J Oral Maxillofac Surg.* 2016;74(6):1181-1185.
84. Harrison R, Hicklin D Jr. Electronic cigarette explosions involving the oral cavity. *J Am Dent Assoc.* 2016;147(11):891-896.
85. Jones CD, Ho W, Gunn E, Widdowson D, Bahia H. E-cigarette burn injuries: comprehensive review and management guidelines proposal. *Burns*. 2019;45(4):763-771.
86. Treitl D, Solomon R, Davare DL, Sanchez R, Kiffin C. Full and partial thickness burns from spontaneous combustion of e-cigarette lithium-ion batteries with review of literature. *J Emerg Med*. 2017;53(1):121-125.
87. Maraqa T, Mohamed MAT, Salib M, Morris S, Mercer L, Sachwani-Daswani GR. Too hot for your pocket! Burns from e-cigarette lithium battery explosions: a case series. *J Burn Care Res.* 2018;39(6):1043-1047.
88. Arnaout A, Khashaba H, Dobbs T, et al. The Southwest UK Burns Network (SWUK) experience of electronic cigarette explosions and review of literature. *Burns.* 2017;43(4):e1-e6.
89. Herlin C, Bekara F, Bertheuil N, Frobert P, Carloni R, Chaput B. Deep burns caused by electronic vaping devices explosion. *Burns*. 2016;42(8):1875-1877. doi:10.1016/j.burns.2017.01.008
90. Tracy P. Florida man killed in first recorded e-cig explosion death. *Daily Dot.* May 16, 2018. Accessed April 2, 2020. www.dailydot.com/debug/e-cig-explosion-death/
91. Howard J, Burnside T. Man dies in e-cigarette explosion, police say. *CNN.* May 15, 2018. Accessed April 2, 2020. www.cnn.com/2018/05/15/health/electronic-cigarette-explosion-death-bn/index.html
92. Naftulin J. A man died after an e-cigarette exploded in his face, and his isn't the first death from these devices. *Insider*. February 6, 2019. Accessed April 2, 2020. https://www.insider.com/man-died-after-e-cigarette-explosion-vaping-risks-2019-2