A Review of E-Cigarettes and Related Health Issues

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Tobacco usage remains a significant public health issue today. The inhalation of smoke from burning tobacco use remains the single largest preventable cause of death and disease in the United States. It is estimated that cigarette smoking kills more than 480,000 Americans each year and that approximately 41,000 die from exposure to secondhand smoke. The impact of smoking related illnesses is also considerable on American society. It is estimated that more than $289 billion per year is spent related to direct medical care for adults and in lost productivity. With the detriment and human toll that smoking has on our society, it continues to be advantageous to strive for reducing smoking and its effects.

Cigarette smoking and nicotine exposure is a co-factor in promoting periodontitis. Periodontitis is a general term used to describe an infectious inflammatory process that may involve one or more structures of the periodontium. Periodontal disease is perhaps the most common chronic infection of humankind. It is estimated that the prevalence of periodontal disease in adults in the United States (ages 20 to 64 years) is 8.5% and is 17.20% in seniors older than 65 years. In 1947, Pindborg noted an association between acute necrotizing ulcerative gingivitis, a form of periodontal disease, and smoking. Several investigators have noted a relationship between smoking and other forms of periodontal disease.

Cigarette smoke is composed of a mixture of more than 4,700 chemical compounds including nicotine, free radicals, and oxidants. Nicotine, although noted for being the addictive component of cigarette smoke, is only one of these various chemical compounds associated with negative health issues, which include periodontitis. The differences with regard to the negative periodontal consequences between exposure to cigarette smoking and e-cigarette smoking will inevitably be demonstrated in the future.

Bouclin et al reported within a review of the literature that periodontal disease is more prevalent in smokers compared to nonsmokers and that neutrophil chemotaxis and phagocytic capacity is reduced in smokers compared to nonsmokers. Other findings noted that smokers had lower IgA, IgG, IgM, and suppressor CD8 lymphocytes compared to nonsmokers. These issues were considered to be factors related to the decreased healing potential of periodontal therapy in smokers compared to nonsmokers. Srinivas et al reported that there was a significant decrease in neutrophil chemotaxis in smokers when compared to nonsmokers.

With regard to the negative effects of singular nicotine upon the periodontium, there are a number of studies reporting various mechanisms. Kang et al, in a study of human gingival fibroblasts, reported that nicotine induces apoptosis through reactive oxygen species generation and caspase-3 dependent pathways. Nakayama et al reported that nicotine suppresses bone sialoprotein through cAMP response element, fibroblast

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growth factor 2 response element, and homeodomain protein-binding site elements as a proximal promoter of the bone sialoprotein gene. Makino et al\textsuperscript{12} reported that nicotine modulates cytokine expression, which in turn regulates immune and inflammatory responses. Wu et al\textsuperscript{15} reported that nicotine may induce production of interleukins-1 beta (IL-1β) and IL-8 via the alpha 7 (α7) nicotinic acetylcholine receptors (nAChR)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway in human periodontal ligament (PDL) cells. Furthermore, with regard to cytokine modulation, Johnson et al\textsuperscript{19} reported that nicotine differentially regulated IL-1 and IL-8 production by gingival keratinocytes. Wang et al\textsuperscript{20} reported the functional expression of α7nAChR/NF-κB in human PDL fibroblasts and rat periodontal tissues. Zhou et al\textsuperscript{21} reported that nicotine deteriorated the osteogenic differentiation of human PDL stem cells in a dose-dependent manner through activation of α7nAChR/NF-κB regulating the Wnt pathway, inducing an osteogenic differentiation deficiency. Furthermore, Breivik et al\textsuperscript{13} reported that nicotinic acetylcholine receptor activation enhances the susceptibility to periodontitis. Tinti and Soory\textsuperscript{22} reported that the results of a human gingival fibroblast and periosteal fibroblast culture study suggested that nicotine induces an oxidative mechanism resulting in down-regulation of 5α-reductase and decreased 5α-dihydrotestosterone.

Electronic Nicotine Delivery Systems
ENDS, also known as e-cigarettes, are battery-powered devices that deliver a heated aerosol of nicotine and lower levels of toxins inhaled in a manner meant to simulate the visual, sensory, and behavioral aspects of smoking conventional combusted cigarettes.\textsuperscript{23,24} There are many variations/brands on the market that differ in design and in the incorporation of ingredients. Despite this variety, they can be generally grouped into the following 3 categories: cigalikes, which resemble conventional cigarettes in shape and size; eGos, which are larger than cigalikes, typically with a removable tank that can be filled with nicotine-containing e-liquid; and mods, which are larger than eGos and extremely customizable.\textsuperscript{25,26} Regardless of the model of e-cigarette used, they share the following common characteristics: (1) a cartridge containing a humectant carrier, such as propylene glycol, often in solution with nicotine without tobacco, glycerin, and tobacco flavoring; (2) a tube into which the cartridge is inserted and through which the user inhales; and (3) a battery-powered heating element causing the humectant to vaporize, forming a mist.\textsuperscript{24,27} Users also need refill cartridges of “juice,” which is the solution that contains nicotine, often in high concentrations, and other materials.

E-cigarettes are being marketed and sold in the United States as another smoke-free tobacco/nicotine alternative to cigarettes, used primarily as an aid for smoking cessation. They are being called tobacco “harm reduction” products. Other examples of smoke-free tobacco/nicotine alternatives to cigarettes include: chewing tobacco, snus and other snuff products, and dissolvables (sticks, strips, and orbs).\textsuperscript{28} Additionally, there are pharmaceutical nicotine replacement therapy products such as patches, gums, lozenges, and inhalers meant for long-term usage.\textsuperscript{28} It has been proposed that e-cigarettes may reduce the risk of tobacco-attributable illness and death by 98% or better, as well as satisfying the smoker’s cravings for nicotine.\textsuperscript{28}

E-cigarettes are unique from other smoke-free tobacco products currently available in the United States. Unlike some of the other smoke-free products, the sales of e-cigarettes are significant and increasing. Much of the sales of e-cigarettes are conducted via the Internet. It is estimated that 30% to 50% of the total e-cigarettes sold are purchased using the Internet.\textsuperscript{29,30} It was estimated that $1.7 billion would be generated through the sale of e-cigarettes by the end of 2014.\textsuperscript{31} It has been suggested that one of the reasons is that the cost compared to that of traditional cigarettes is fueling sales. The cost of a traditional tobacco cigarette is approximately $1.5/pack while an equivalent amount of e-cigarettes costs about $1.50.\textsuperscript{31} It is estimated that there are 2.5 million e-cigarette smokers in the United States;\textsuperscript{32} 6.7% of the adult population and 10% of the high school population have tried them.\textsuperscript{32}

Despite their increasing sales, e-cigarettes are associated with regulatory ambiguity by the FDA and do not carry warnings about cancer or other diseases as do other tobacco products. For now, despite being widely available in the United States, the FDA has not regulated e-cigarettes the way it does tobacco and traditional tobacco cigarettes.\textsuperscript{33} It is unclear as to whether ENDS should be regulated by the FDA's traditional Center for Drug Evaluation and Research, which is the branch that regulates medicinal nicotine products, or the new Center for Tobacco Products, which regulates reduced harm products.\textsuperscript{24} Current FDA regulations state that ENDS may not be marketed as safer alternatives to cigarettes or as smoking cessation devices but must instead be sold as smokeless tobacco products.\textsuperscript{27} This, too, is controversial because ENDS only contain a trace amount of tobacco in the flavoring, added to the liquid refill cartridge. Furthermore, tobacco products including e-cigarettes must disclose ingredients found in the e-cigarette liquids, proof of safety of those ingredients, and regulation of the devised use to vaporize and deliver the liquid.\textsuperscript{34,35} States are developing their own set of rules and regulations on how to restrict the sale and use of e-cig-
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Ate, including ban of sales to minors. In other countries, such as Australia, Canada, Singapore, and Brazil, ENDS have been banned due to a lack of safety and efficacy data. A primary concern about e-cigarettes is the safety to the general public, not only for the user but also for those in the vicinity of the user. Currently, there are no product standards regarding criteria of ingredients, quality, manufacturing, and labeling of e-cigarettes. This means that significant variability exists among the 460 brands (and counting) of the e-cigarettes on the market in the United States. Studies that have assessed the physiological effects of e-cigarettes have found as a whole that they may be less harmful than traditional cigarettes regarding less inhalation of compounds and fewer toxins. Some common positive physiological changes were reported to be associated with smoking e-cigarettes, such as less coughing, fewer sore throats, improved fitness, reduced bad breath, “improved chronic obstructive pulmonary disease,” “asthma relief,” and “cleared bronchitis.” Conversely, some negative physiological changes were reported associated with smoking e-cigarettes include the following: increases in blood pressure and heart rate, coughing, mouth and throat irritation, “tightening of the lungs,” and “difficulty breathing.”

The concentration of nicotine in the cartridges of e-cigarettes varies, ranging in strengths from zero to 24 mg or higher based on the user’s preference. Studies have found variability between the concentration of nicotine listed on the label compared to what was actually found in the liquid refill cartridge. The FDA stated that there is too much variability in the amount of nicotine delivered per puff of any of the e-cigarette cartridges for them to be considered safe. It is quite possible that at the higher concentrations, an environment exists for nicotine toxicity. Nicotine may be absorbed through the skin, mucous membranes, gastrointestinal tract, and the airway. Further studies need to be done to determine where most of the nicotine from e-cigarettes is primarily absorbed; the airways, oral cavity, or the alveoli. Signs of toxicity include dizziness, nausea, vomiting, changes in heart rate, confusion, and fatigue. It has been recommended that additional regulations should focus on those things that could potentially lower the risks associated with e-cigarettes. For example, the liquid refill cartridges should be childproof and users must take care to store them out of the reach of a child. This would ensure that a child would not potentially be able to ingest large doses of nicotine that could potentially be lethal.

Although the concentration of nicotine in the liquid refill cartridges is high, there exists a low potential for addiction from usage. This is despite nicotine being a highly addictive substance. The rate at which nicotine enters the central nervous system after being inhaled is low and takes several minutes, comparable to that found in nicotine replacement products such as patches, chewing gums, sprays, and inhalers. In contrast, when smoking a tobacco cigarette, the nicotine inhaled reaches the central nervous system within seconds. In addition, the level of nicotine in the serum is also lower in those who use e-cigarettes compared to those who smoke traditional tobacco cigarettes.

The e-cigarette cartridge refills contain toxic levels of nicotine. The nicotine from the aerosol vapors or liquid cartridge refill may remain on surfaces for extended periods of time, reacting with nitrous acid found in the ambient environment to produce tobacco-specific nitrosamines (TSNAs). TSNAs are known carcinogens. “Thirdhand smoke” exposure of toxins and carcinogens can occur through the skin, ingestion, or breathing and can be potentially hazardous to us all, long after the user has gone. Researchers have found the risk for “secondhand smoke” exposure as a result of using e-cigarettes to be very low. E-cigarettes produce very small exposures of pollutants such as volatile organic compounds, carboxyls, polycyclic aromatic hydrocarbons, and nicotine compared to traditional tobacco cigarettes. Despite these findings, there is still a belief that e-cigarettes should be subject to the “Clean Indoor Air Act” in the same manner as traditional tobacco cigarettes.

Glycerin and propylene glycol are components of the e-cigarette liquid cartridges. Both have properties that irritate mucous membranes, particularly of the upper airways and the eyes. Studies have been done to evaluate the effect of these components on human embryonic stem cells, mouse neural stem cells, and human pulmonary fibroblasts. Findings confirmed that embryonic stem cells and neural stem cells in general were more sensitive than human pulmonary fibroblasts to the products; however, more research is necessary to determine whether cytotoxic effects are seen in humans over a long period of time.

Exposure to nicotine and the potential for its deleterious effects, such as addiction and toxicity, are some of the real concerns associated with children and teens using e-cigarettes. Despite bans being in place in many states making it prohibitive to sell e-cigarettes to minors, there are youngsters who are gaining access to them via Internet sales. The many varieties of brands and additions of enticing flavors—such as licorice, strawberry, chocolate, fruit, and mint—and their low cost, make them attractive to children and teens. Researchers have found the numbers of youth in grades 6 through 12 using e-cigarettes doubled from 3.3% to 6.8% from 2011 to 2013. Equally con-
cerning, they noted that youth, like adults, often practice dual use of both e-cigarettes and traditional tobacco cigarettes. Studies have also shown, in adolescents, a strong correlation between e-cigarette usage and male gender, being tobacco smokers, and having parents who smoke. It is hoped that e-cigarettes might be used as an alternative to traditional tobacco cigarettes, in an effort to promote smoking cessation. Often, however, particularly with heavy smokers and those who practice dual-smoking of both traditional tobacco cigarettes and e-cigarettes, that has not been the case. Studies have found that e-cigarettes are not associated with, or have a very low association with, quitting traditional tobacco cigarettes. E-cigarette usage among the college-aged has shown that often they are using them not out of a motivation to quit smoking but because it is something new, something else to smoke. As more and more brands come to market, there has been a push from manufacturers to actually stop promoting e-cigarettes as an adjunct for smoking cessation. They want consumers to readily purchase their products, with the intent of using them for as long as they smoked traditional tobacco cigarettes.

**CONCLUSION**

ENDS or e-cigarettes are making an impact on the public health of our society. It is clear that additional regulatory and quality control measures need to be undertaken regarding ingredients, quality, labeling, and manufacturing of e-cigarettes. Furthermore, long-term, rigorous studies are needed in order to gain additional insight regarding safety and effects on humans. Until more information is available, no conclusions can be made about the potential dangers or usefulness of e-cigarettes. As health care professionals, dental personnel need to be aware of the literature regarding smoke-free tobacco/nicotine alternatives to cigarettes, including ENDS/e-cigarettes. This will enable us to inform our patients and allow us to guide and counsel our patients.

**References**

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1. What is the single most preventable cause of death and disease in the United States?
   a. Alcohol consumption.
   b. Suicide.
   c. Homicide.
   d. Cigarette smoking.

2. Periodontal disease is more prevalent in smokers than nonsmokers.
   a. True.
   b. False.

3. Which category of electronic nicotine delivery system (ENDS) most resembles conventional cigarettes?
   a. Mods.
   b. Cigalikes.
   c. eGos.
   d. None of the above.

4. An ENDS consists of how many components or characteristics?
   a. 1.
   b. 2.
   c. 3.
   d. None of the above.

5. It was estimated that the sale of ENDS would generate how much money by the end of 2014?
   a. $500,000.
   b. $1.0 million.
   c. $7.3 million.
   d. $1.7 billion.

6. There are currently approximately how many brands of ENDS on the market in the United States?
   a. 280.
   b. 460.
   c. 720.
   d. None of the above.
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7. What are signs of nicotine toxicity?
   a. Dizziness.
   b. Fatigue.
   c. Nausea.
   d. All of the above.

8. The potential for nicotine addiction from using ENDS is high.
   a. True.
   b. False.

9. The risk of exposure to tobacco-specific nitrosamines through the skin and by ingestion is called?
   a. “First hand smoke” exposure.
   b. “Second hand smoke” exposure.
   d. None of the above.

10. The addition of what substances are making ENDS attractive to children and teens?
    a. Flavorings.
    b. TSNAs.
    c. Glycerin.
    d. Nicotine replacement therapy.
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3. ☐ a  ☐ b  ☐ c  ☐ d

4. ☐ a  ☐ b  ☐ c  ☐ d

5. ☐ a  ☐ b  ☐ c  ☐ d

6. ☐ a  ☐ b  ☐ c  ☐ d

7. ☐ a  ☐ b  ☐ c  ☐ d

8. ☐ True  ☐ False

9. ☐ a  ☐ b  ☐ c  ☐ d

10. ☐ a  ☐ b  ☐ c  ☐ d

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