The Anesthetic Implications for the Patient Who Vapes

A DNP Project Presented to the Faculty of the
Nicole Wertheim College of Nursing and Health Sciences

Florida International University

In partial fulfillment of the requirements
For the Degree of Doctor of Nursing Practice

By

Lindsey H. Bell MSN, BSN, FNP-BC, AGACNP-BC, APRN

Supervised By

Charles Buscemi PhD, APRN, FNP-BC, CWCN

Karina G. Grubbs DNP, CRNA, APRN

Approval Acknowledged: DocuSigned by: Ann Miller A986D8685093471... , DNA Program Chair

Date: 11/4/2024

Approval Acknowledged: Signed by: 27267E9FF76F460... , DNP Program Director

Date: 11/4/2024

Abstract

Background: According to data from the National Center for Health Statistics and the Centers for Disease Control and Prevention (CDC), about 8.1 million adults and 2.55 million adolescents in the United States (US). use electronic cigarettes (ECs). With the number of vaping individuals in the US increasing and the damage done by ECs to the lungs being so hazardous, in 2020, the CDC was forced to declare an outbreak of Electronic Cigarette or Vaping Associated Lung Injury (EVALI). EC users, who consider themselves distinct from traditional cigarette smokers, identify as vapers. This may present challenges for anesthesia providers in assessing smoking status before surgery, potentially leading to complications during the perioperative period. This literature review examined the acute and chronic side effects of ECs and their impact on surgical patients under anesthesia. This literature review also offered recommendations for anesthesia providers managing patients who vape.

Methods: For this quality improvement project, anesthesia providers at a large urban teaching hospital in south Florida received an educational intervention tool with evidence-based information. Anesthesia providers were educated on the negative side effects associated with the use of ECs for surgical patients and potential perioperative management techniques that can be utilized to avoid complications. A survey determined the knowledge of providers before and after the educational intervention. Outcomes were measured by evaluating the variations in the anesthesia providers' knowledge of the negative side effects associated with electronic cigarettes and perioperative management techniques for this patient population, pre and post intervention. In order to generate reports, Qualtrics® software was used to create the surveys and analyze the data.

Results: An educational intervention was designed and delivered via email to anesthesia providers at a large urban hospital in south Florida. The goal of this educational intervention was to improve their knowledge of the anesthetic implications for patients who vape. Pre- and post-test scores were compared and evaluated. Overall, there was an increase in participant knowledge following the educational intervention.

Discussion: Data collected from the surveys showed that participant knowledge regarding the neurological, ocular, oropharyngeal, and cardiopulmonary effects from vaping and the anesthetic implications for each of these organ systems increased. The most significant increase in knowledge was regarding airway hyperresponsiveness and EC liquid flavorings. A small sample size and the time frame for responses were limitations of this project.

Conclusion: Evidence-based research shows that patients who vape have an increased risk for complications during the perioperative period, especially when their social history is undisclosed. Results showed an increase in anesthesia provider knowledge regarding the importance of obtaining a thorough preoperative evaluation in patients who vape, the potential complications that can occur during the perioperative period, and the anesthetic implications that can allow for increased patient outcomes in spite of this social comorbidity. Continued research into vaping can lead to improvements in patient outcomes by standardizing preoperative evaluations and perioperative management techniques for patients who vape.

Keywords: Electronic cigarettes, vaping, electronic cigarette liquid, health hazards, and anesthesia

Table of Contents

Abstract 2
Problem Identification 5
Background 5
Scope of the Problem 10
Consequences of the Problem 12
Knowledge Gaps 13
Proposed Solution 13
Methodology 15
  Eligibility Criteria 15
  Information Sources 15
  Search Strategy 16
Results of Literature 17
  Study Characteristics 17
  Results of Individual Studies 17
    Neurological 17
    Ocular 24
    Oropharyngeal 29
    Pulmonary 38
    Cardiovascular 44
  Results 56
  Discussion 58
  Conclusion 63
Purpose/PICO Clinical Questions/Objectives 64
  PICO Question or Purpose 64
  Primary DNP Project Goal 65
Goals and Outcomes 68
  Specific 68
  Measurable 68
  Achievable 68
  Realistic 69
  Timely 69
Program Structure 69
  Strengths 70
  Weaknesses 70
  Opportunities 71
  Threats 71
Methodology of Quality Improvement 72
  Setting and Participants 72
  Description of Approach and Project Procedures 72
  Protection of Human Subjects 73
  Data Collection 73
  Data Management and Analysis 74
Results 74
  Demographics 74
  Pre-Test Knowledge of Anesthesia Implications for Patients Who Vape 76

Post-Test Knowledge of Anesthesia Implications for Patients Who Vape 77
Summary of Data 79
Limitations 84
Discussion of the Results with Implications for Advanced Nursing Practice 85
Conclusion 87
References 88
Appendix A: Literature Review Characteristics Table 94
Appendix B: IRB Exemption 122
Appendix C: QI Project Consent 123
Appendix D: Recruitment Letter 126
Appendix E: Pre-Test/Post-Test 127
Appendix F: QI Educational Module 131

Problem Identification

There is well documented evidence surrounding the perioperative risks associated with cigarette smoking, the benefits of cessation of cigarette smoking prior to receiving anesthesia, and the importance of performing a high-quality preoperative anesthesia assessment of cigarette smoking status to quantify perioperative risk and determine intraoperative anesthetic management.[1, 2, 3] While the evidence surrounding the health hazards of electronic cigarettes (ECs) continues to rise, their sustained use by patients who undergo surgical procedures remains high.[4] There is a constant onslaught of new information and data that can be derived from the literature, so it can be assumed that a knowledge deficit could exist among anesthesia providers in regards to the health hazards of ECs. Additionally, unlike traditional cigarettes, there is no current standardized preoperative screening tool to identify patients at risk for intraoperative anesthesia complications.[4] To compound these factors, the public misconception about ECs and vaping is that they are healthier than traditional cigarettes, which may lead to their use going unreported in the preoperative period.[5] These factors combine to create the perfect storm of increased perioperative complications that appear to share many of the avertible problems observed with patients who admit to traditional cigarette smoking when a thorough preoperative anesthesia evaluation and assessment is performed.[3, 6]

Background

The health hazards associated with the use of ECs impacts multiple organ systems in humans and animals. The research shows that patients who use ECs experience increased airway resistance, decreased oxygen saturation, and a decrease in fractional exhaled nitric oxide, which indicates lung inflammation and oxidative stress.[7] The vapor from ECs causes an interruption in pulmonary gas exchange and impairs immune function, increasing the risk for viral or bacterial

infection.[8] Components found in the liquid aerosolized into the pulmonary system are the main source of pulmonary damage.[9] These components have been found to cause increased airway resistance, inflammatory hyperreactivity, impaired mucociliary clearance, increased oxidative stress, impaired immune response, disruption of surfactant function due to conformational change, and impaired gas exchange related to alveolar and parenchymal lung changes.[9] Review of the literature found that individuals who use ECs that present to the hospital for pulmonary complaints often are diagnosed with EVALI, which is a disease process similar in progression and mortality rate to adult respiratory distress syndrome (ARDS).[10] Diagnoses following closely behind EVALI are pneumonia, pneumothorax, and exacerbated asthma attacks.[10] These pulmonary consequences impact intraoperative ventilatory management, emergence, and extubation following surgical procedures.

The research shows that cardiovascular consequences of EC use lead to an increase in heart rate, systolic blood pressure, and systemic arterial stiffness.[7, 8] The increase in arterial stiffness, while reversible in healthy patients, is indicative of elastic fiber loss and increased arterial wall fibrosis, which mimics disease processes like atherosclerosis.[11, 12] The result is increased cardiac load, reduced coronary perfusion, and increased risk for MI.[11] Components in the liquid vapor generate carcinogenic compounds when heated and causes endothelial dysfunction through multiple complex mechanisms.[11] Research has shown that ECs cause decreases in cardiac vagal tone and increases in sympathetic tone following use, which increases morbidity and mortality through development of cardiac dysrhythmias; nicotine containing ECs cause added effect.[13, 14] The literature shows an association between EC use, increased reactive oxidative species (ROS), and decreased protective compounds against ROS such as vitamin E and nitrogen oxide species.[13] This can lead to endothelial dysfunction, leading to disease

processes such as hypertension.[13] The use of ECs in the short term has been shown to increase both systolic and diastolic blood pressure, which further impacts the development of hypertension.[15] Research has shown an increased risk for MI and heart failure due to components in EC liquid.[16]

In animal models, the particles found within the liquid of ECs are shown to cause neurologic damage such as epigenetic alterations, mitochondrial dysfunction, inflammation, oxidative stress, and disruption of neurotransmitter production and homeostasis.[17] Vitamin E acetate, a common additive to EC liquid, is predicted to penetrate the human blood brain barrier via passive diffusion, wreaking havoc on the central nervous system (CNS).[8] Vitamin E acetate byproducts cause CNS impairment and inflammation of neurovascular tissue.[8, 18] Acute nicotine intoxication increases likelihood of seizures.[18] These factors are important for the anesthesia provider in the emergence and post-operative recovery phase.[19] Negative outcomes from difficult or delayed emergence due to the neurologic side effects of components of the liquid in ECs can result in longer hospital stays, dangerous self-extubation, unintentional removal of medical devices such as catheters, and injury.[19] Caring for the eyes is part of the anesthesia provider's responsibility. ECs can cause unstable tear film, ocular surface dryness, and an inflammatory response in corneal epithelial cells which increases the risk for corneal abrasions during anesthesia.[20,21] Nicotine induces nystagmus and causes vasoconstrictive effects on the blood flow to the eyes which can increase the risk for injury in the form of cortical blindness or retinal ischemia.[21, 22]

The use of ECs has been shown to negatively impact periodontal health and patients who vaped were shown to have increased plaque, tooth decay, and bleeding of the oral cavity with the temperature and contents of the vapor causing mouth lesions and ulcers.[8, 23] The components of

EC vapor increases oral inflammation and disrupts normal flora resulting in the development of tooth loss, infection, and oropharyngeal cancer which can complicate laryngoscopy and intubation.[24] The components found in the liquid of ECs affects gastrointestinal health by causing inflammation to the mucosa, which alters motility and causes nausea, vomiting, and diarrhea and increases a patient's risk for aspiration on induction and post operative nausea and vomiting.[8] ECs cause liver enzymes to increase due to damage related to oxidative stress and increased accumulation of fat in the liver resulting in altered metabolism of many anesthetics.[8] The kidneys show signs of damage with ECs with hyperuricemia, increased creatinine levels, and albuminuria along with elevated inflammatory markers that affect the clearance of anesthetic agents.[8] Individuals who use ECs were at higher risk for bladder cancer and exposure to carcinogenic compounds.[25] Mice exposed to vapors from ECs were at increased risk for kidney disease due to cellular changes occurring in the kidneys.[26] Reproductive issues are associated with ECs are hormonal imbalance, dysfunction of gonads, reduction in spermatogenesis and embryo implantation, and diminishing milk production.[8]

The impact of ECs on musculoskeletal health result in increased osteoporosis risk, muscle cell damage, and osteotoxicity, which can make positioning patients for surgical procedures challenging.[8] Exposure to components of liquid found in ECs has a negative impact on bone cell viability and impairs function of osteoblasts.[27] The use of ECs causes delayed wound healing in surgical patients due to decreased blood flow and tissue regeneration with increased likelihood of surgical wound infections.[28]

With acute use of ECs, the literature shows hematological changes such as worsening endothelial function, increasing blood viscosity, and increasing oxidative and inflammatory stress markers.[8] The literature shows that there is an increase in platelet aggregation in users of

ECs, which increases the likelihood of thrombosis, ischemia, and potential infarction.[13] The evidence surrounding the immunosuppressive effects of ECs and the exposure to the chemicals found in the liquid in ECs has shown DNA damage due to oxidative stress in head and neck cancers.[29] There are several carcinogens found in the urine of individuals who use ECs, which has links to several different forms of cancer in humans.[30]

The components of the liquid that is added to the EC that is then inhaled into the mouth and lungs contains many additives like propylene glycol, glycerin (vegetable glycerin or glycerol), water, flavoring, and sometimes nicotine or cannabis products including an oil containing the psychoactive ingredient tetrahydrocannabinol (THC).[31] Nicotine is either isolated from the tobacco plant or made synthetically.[31] The isolated nicotine contains known carcinogens while the synthetic nicotine has been altered into a more potent product, nicotine salts, which is used in newer EC products to produce a higher concentration of nicotine to be absorbed by the user.[31] The use of THC products varies widely, and it is difficult to determine the exact concentrations in which they are used.[31] The vaping of THC products through an EC is better known as dabbing.[31]

The inhalation of these products, such as propylene glycol, vegetable glycerin, and humectants, can cause pulmonary irritation.[31] When heated, these products break down and cause severe airway epithelium injury and decrease the amount of oxygen that can be absorbed from alveoli into arterial blood.[32] The inflammatory cell counts in the lung and urinary biomarkers increase as a result of inhalation of propylene glycol and vegetable glycerin.[32] Detectable measurements of heavy metals and microbial contaminants in the liquid can cause severe consequences in the lungs and the rest of the body.[31] Just a few of the heavy metals and microbial contaminants found in the EC liquid are metals such as aluminum, lead, and nickel

with bacterial endotoxins and fungal glucans also discovered.[33] Carcinogenic compounds such as formaldehyde, acetaldehyde, and acrolein along with organic chemic compounds such as benzene, toluene, and styrene are also found in the EC liquid, which lead to many types of cancer and lung diseases such as Chronic Obstructive Pulmonary Disease (COPD).[34]

There are over 8000 flavorings on the market for ECs, and not all of them have been studied to determine safety profile.[34] The flavorings are grouped into desserts, fruity flavors, sweets, popular beverages such as coffee or alcohol, spices and nuts, mint and tobacco, and an unflavored option.[34] Flavorings increase appeal to the EC product and changes perceptions surrounding EC use in younger, more vulnerable populations.[31] Flavorings found in the EC liquid are made using products such as diacetyl, guaiacol, geraniol, menthol, ethyl maltol, and 2,3-pentanedione.[31] Diacetyls are known to cause bronchiolitis obliterans, popcorn lung, which causes a disease process very similar to COPD.[33] Interestingly enough, certain flavors have significantly worse toxicity in the lungs than others.[34] These flavors are mint or menthol, cinnamon, and strawberry.[34] The adverse effects from these flavors include increased oxidative stress, inflammatory biomarkers, and cytokine release in the lungs.[34] Reduced cell proliferation and increased airway hyperresponsiveness are toxic side effects noted from these popular flavor choices.[34]

Scope of the Problem

Martins et al. reviewed the global frequency of EC users and following the inclusion of 43 articles and 1.2 million participants and found that 10.7% were EC users with the age range of higher percentage users being ages 18-24 years.[35] Males were the most common gender to use ECs, and the countries with the highest prevalence of EC users were Croatia (52.88%), New Zealand (49.62%), Poland (45%), and the US (34.8%).[35]

The perception among adolescents and young adults regarding the use of ECs is that they are a healthier alternative and that an individual who vapes does not smoke.[36] The addictive nature of using ECs comes not just from the addition of nicotine or other additives but from the perceived throat hit or harshness of the liquid product and speed at which the effect of the nicotine or other additives occurs.[37] Other notable factors include the aroma or taste as well as the auditory sound heard upon inhalation.[37] Social inclinations, frank curiosity, stress, and fear of being left out are usually how adolescents begin using ECs.[37] Over time, the oral fixation and behavioral or sensory dependence on the EC is only heightened by the addicting nature of the additives in the liquid being inhaled.[37]

Use of ECs among adolescents is associated with accelerated health and mental health problems. Adolescents who use ECs are shown to have higher rates of mental health problems such as depression, anxiety, suicidal ideations, eating disorders, conduct disorders, and impulsivity or perceived stress.[38] Adolescents who use ECs have also been shown to be at a higher risk for alcohol and drug abuse.[39] The most significant data regarding this vulnerable population and the use of ECs is the degree and acceleration at which life-threatening lung injury is occurring. Since 2020, over 2,500 patients have been hospitalized due to EVALI.[40] Of these 2,500 patients, 68 died with 15% of these deaths being patients younger than 18 years of age.[40] The development of chronic lung disease as young individuals is another factor to consider as the literature supports the conclusion that adolescents who use ECs have a higher risk for developing chronic cough, asthma, or COPD.[41,42]

Another high-risk population that perceives that ECs are a safe and effective way to quit smoking traditional cigarettes and are experiencing detrimental effects are pregnant women.[43] The literature found that women who use ECs during their pregnancy are at a higher risk for

having a high-risk birth in the form of preterm or low birth weight baby, birth defects, and placental (previa or abruption) issues, or pre-eclampsia.[43] EC use during pregnancy was also associated with a higher risk of fetal death in the form of miscarriage, abortion, or ectopic or tubal pregnancy.[43]

Consequences of the Problem

Several published case studies demonstrated the detrimental effects of undergoing anesthesia without previous knowledge of vaping history.[44, 45, 46, 47] The emphasis of many of the case studies surrounds the development of EVALI.[44] This often occurs with young patients who appear healthy and with no other comorbid pulmonary factors that would lead the anesthesia provider to anticipate any intraoperative or postoperative pulmonary complications.[44] These cases occur most often in the adolescent population during the postoperative period resulting in unanticipated intensive care unit (ICU) admissions due to respiratory failure and increased risk of perioperative pulmonary morbidity.[48] In addition to the potential outcome involving life-threatening pulmonary failure and ICU admission, there is the increased risk for delayed surgical wound healing and development of infection or sepsis.[49]

When the use of ECs is not disclosed during the preoperative assessment and evaluation, important information that can be used to manage intraoperative anesthetic administration or make diagnoses when complications occur, can be missed.[50] Misdiagnoses can delay treatment and cause further damage.[50] This can be especially challenging when attempting to determine causes of medication interactions with components found in the EC liquid.[50] Certain chemicals can interact with the anesthetics commonly delivered during the administration of a general anesthetic that may warrant increased doses of sedatives or opioids.[50]

Knowledge Gaps

Current knowledge gaps in the literature regarding the use of ECs and their impact on the administration of anesthesia is the interaction of the ingredients found in the liquid vapor and the volatile anesthetics that are administered during general anesthesia. Additionally, the interaction of the humectants and volatile anesthetics and how this interaction impacts cardiopulmonary health are unknown. A high-risk medication commonly used in the administration of anesthesia is the class of paralytics or muscle relaxants. There appears to be a lack of data in the literature regarding any interactions that may occur with the ingredients found in ECs and these high-risk medications that are used on a daily basis in the anesthesia provider's line of work. The knowledge needed to fix this problem would involve studies being performed on animals to determine the interactions with these harmful chemicals found within ECs and their effect on the body when administered concurrently with commonly used anesthetics such as sedatives, opioids, and muscle relaxants. There is potential for a retrospective type of project with a review of anesthesia records to include vitals and medication administration to determine if interactions intraoperatively arose or increased consumption of medications occurred with a patient's known history of EC use.

Secondhand or passive effects on children of patients who use ECs is also an area of the literature that contains a knowledge gap. While preliminary studies are being done to determine the effect that vapor from ECs have on the environment and on the potential hazards of secondhand vapor, more research needs to be performed.

Proposed Solution

One of the most important aspects to this project is to educate anesthesia providers on the systemic effects of ECs and the anesthetic implications surrounding the patient populations who

acutely use ECs, chronically use ECs, and those who modify or use varying additives, like THC, in their ECs. It is also imperative to consider and anticipate the potential systemic effects of nicotine, THC, and the other components of the liquid found in ECs and the possible complications that might arise in the perioperative period.

Very few current preoperative assessment tools exist for patients who use ECs. One that was found within the literature by a large urban teaching hospital located in South Florida has shown clinically significant improvements in the identification of patients who use ECs and their likelihood of adverse perioperative outcomes.[50] The quantification of use (never, former, or current), type of EC liquid consumed, which is additive specific, use per day, and number of years of vaping history, are included in this pilot project with the addition of any treatment for cessation of vaping, a readiness for change assessment, as well as an indicator for positive passive exposure.[50]

When determining risk cardiopulmonary risk assessment with traditional cigarettes the quantification of use, use per day, and number of years of smoking history is established.[51] An important question that is asked of current traditional cigarette smokers is if they have abstained from smoking prior to their procedure and if so, for what duration of time as there are known benefits to abstinence from smoking prior to surgery.[52] This guides the anesthesia provider in determining which methods will be best suited for this particular patient in order to deliver safe and effective anesthesia during the perioperative period.[52] Given the duration in which the patient has abstained from smoking, if they have at all, will provide valuable insight as to the type of anesthetic to deliver (regional versus general versus monitored anesthesia care), the type of inhalational agents to use or not use, intravenous medications that can be utilized to prevent

unwanted side effects associated with nicotine or tobacco products, and the anticipation of potential intraoperative events.[52]

A similar assessment can be utilized for patients who use ECs; however, the quantification of nicotine or "cartridges per day" must be calculated to accurately understand risk, anticipate complications, and provide safe anesthesia.[53] The importance lies in how to properly assess and evaluate patients who use ECs and if further pulmonary or cardiac testing is indicated based on use to eliminate or anticipate perioperative complications when delivering anesthesia.[52]

Methodology

Eligibility Criteria

The studies that were evaluated for this literature review were selected based on the inclusion and exclusion criteria which best contributed to the stated objectives. Inclusion criteria were comprised of studies that were in English and with full-text availability. Exclusion criteria were comprised of studies that did not involve the health hazards associated with the use of ECs, that analyzed the health hazards of cannabis or THC products in the EC liquid, or discussed EC injury linked to device related mishaps. Clinical database sources used to guide research were accessed via Florida International University library services.

Information Sources

Based on the clinical question, the following search keywords were identified using the appropriate Boolean operators and search symbols: electronic cigarette toxicity, health hazards, electronic nicotine delivery systems, and chronic or acute effects. The databases utilized for the search included PubMed, The Cumulative Index to Nursing and Allied Health Literature (CINAHL), and MEDLINE (ProQuest).

Search Strategy

The key search terms were further expanded to include “Health hazards” OR “health risks” OR “health problems” AND “electronic cigarettes” OR “vaping device” OR “electronic nicotine delivery systems” OR “E-Cig”. The PubMed search produced 9,835 articles, CINAHL returned 1,039 articles, and MEDLINE provided 3,662 articles. To ensure the most applicable and current articles were reviewed, only articles published from 2019 to 2023, available in full text, and those written in English were included. This filtered the results down to 312 articles for PubMed, 573 articles for CINAHL, and 240 articles for MEDLINE. Duplicate articles were removed, and the search was narrowed further for all 3 databases to exclude articles that discussed prevention or cessation of use, prevalence or cost, and perceptions or advertisements. Titles were screened and excluded if they did not meet inclusion criteria. Articles that included health effects of switching from TC to ECs, evaluated cell lines and not animals or humans exposed to EC vapor, or discussed the pharmacokinetic profiles of various name brand ECs were excluded. Studies that were not completed or were letters to the editor were excluded. The populations accepted were pediatric, adolescents, and adults.

The abstracts of 26 articles were screened and reviewed. Following abstract assessment, 18 articles met the criteria and were further evaluated by reading the full text. Articles were removed if they contained patient populations that were dual EC and TC users but were included if participants had not used a TC in over 1 year. Following full text review, 11 articles were chosen for this review.

Results of Literature

Study Characteristics

The 11 articles chosen for this literature review evaluated the acute and chronic effects of EC use on various organ systems and the implications of these effects that should be considered by the anesthesia provider to optimize the anesthetic plan for patients undergoing surgical procedures.

Results of Individual Studies

Neurological

The first article, published by Alasmari et al[54] in 2019, evaluated the concentration of inhibitory and excitatory neurotransmitters in the frontal cortex and striatum of mice after long term exposure to EC vapor. This quasi-experimental study examined the effects of daily exposure to EC vapor in male C57BL/6 mice that were 6-8 weeks old over a 6-month period. The EC used was classified as a 2.4-ohm plastic, refillable, cartomizer tank. EC liquid was flavorless, without additives, and contained 50% vegetable glycerin, 50% propylene glycol, and 24mg/mL of nicotine. Mice were placed in soft mesh restraints so that only their noses were exposed to a central channel through which the intervention group, containing 10 mice, received EC vapor and the control group, also containing 10 mice, received environmental air. EC vapor was created by activating the battery with application of negative pressure at 2L/min for 1 second, followed by continuous negative pressure at 1L/min for 3 additional seconds. Mice inhaled EC vapor or air, respectively, for 4 seconds every 20 seconds, for 1 hour every day, 5 days per week, for 6 months. After 6 months, mice were anesthetized, euthanized via terminal intra-aortic bleed, and their brains dissected to isolate the frontal cortex and the striatum. High-performance liquid chromatography with electrochemical detection was performed to determine

the levels of glutamate, glutamine, GABA, dopamine, and serotonin in the frontal cortex and striatum of both groups.

There was a total of 10 male mice split into equal groups: 5 mice in the EC group and 5 mice in the air or control group for this study. Six months of chronic exposure to EC vapor caused a statistically significant decrease in the concentration of dopamine in the striatum but not in the frontal cortex. There were no significant changes in the serotonin concentrations in the frontal cortex or the striatum. The mice who had been chronically exposed to EC vapor had statistically significant increases in glutamate concentration in the striatum but not in the frontal cortex. The chronic exposure to EC vapor caused a statistically significant increase in the glutamine concentration in both the frontal cortex and the striatum. Finally, the exposure to EC vapor over the course of 6 months induced a statistically significant decrease in the levels of GABA in the frontal cortex but not the striatum.

The limitations of this article included a small sample population size that is specific for species and gender. This limits the ability to generalize the study's findings to other species and does not account for the potential gender differences in response to the intervention. Another limitation is that the controlled exposure conditions does not accurately mimic the setting in which ECs are used. The focus on specific neurotransmitters in the frontal cortex and striatum is also a limitation, as other areas of the brain may contain relevant findings in regard to this intervention. Lastly, because this is an animal study, an important limitation to consider is that the findings in animal research does not always translate to humans. Additional research would need to occur to confirm these findings amongst humans.

The second article, published by Heldt et al[55] in 2020, determined the impact of long-term exposure of EC vapor on the function of the blood brain barrier (BBB). This was done by

measuring the expression of vascular and inflammatory markers, permeability of the BBB and microglial activation, and the interaction between leukocytes and endothelial cells. Researchers also measured affective state and cognitive function. Similar to Alasmari et al, the quasi-experimental design and examined the effects of daily exposure to EC vapor in male C57BL/6 mice that were 8 weeks old. Unlike Alasmari et al, who examined effects over a 6-month period, Heldt et al had an 8-week exposure period. While Alasmari and colleagues examined an EC intervention group and a room air control group, Heldt et al compared 4 groups: EC groups with and without nicotine, a TC group, and a control group with room air. The EC used was classified as a 1.8-ohm nichrome cotton-wick dual-coil unit, a different model than Alasmari et al, who utilized a 2.4-ohm device. Two different commercially purchased tobacco-flavored EC liquids with concentrations of either 0 or 18mg/mL of nicotine were used, which differed from Alasmari et al, where the concentration of nicotine was 24mg/ml. Distinct from Alasmari et al, the components of the EC liquid were not disclosed. The TCs used were 1R6F reference cigarettes provided by Kentucky Tobacco Research and Development Center but their nicotine content or composition were disclosed. During the exposure, individual mice were placed in TE-2e smoking apparatus and exposed to either nicotine containing (EC1.8%) or nicotine-free EC (EC0%) vapor, TC smoke, or room air. This varies from Alasmari et al who exposed only the noses of the mice to the vapor or air. EC vapor was created by generating a 4-second puff, approximately 35mL, every 30 seconds with 6L/min of total airflow, 2 hours every day, 5 days per week, for 8 weeks. TC smoke was created by burning 2 TCs concurrently with 28 seconds of time between puffs with approximately 3.7L/min of airflow. The room air control group experienced similar flows, management, and placement into the TE-2e apparatus. These flows and puff times were based on pilot studies, which correlated serum cotinine levels in previous

EC and TC models to determine comparable levels of exposure. Unlike Alasmari et al, all groups underwent behavioral tests 2-4 hours following exposure to their various substances. To determine if body weight and biomarker trends noted in humans were similar to mice, all mice were weighed at 2-week intervals prior to daily exposure and blood collection via submandibular bleed occurred at 1-hour post-exposure, and at weeks 1, 3, 5, and 7 of exposure to measure serum cotinine levels. After 8 weeks, mice were euthanized by decapitation under isoflurane anesthesia 24 hours following the last EC, TC, or air exposure. Cerebral micro-vessel isolation occurred, and RNA isolation was performed and characterized. Isolated RNA was reverse transcribed, sequenced, and aligned with the mouse genome to identify and map differentially expressed genes. Histology was performed on the lung, frontal and parietal lobes of the left hemisphere of the brain, and the basal ganglia. This shows some similarities to Alasmari et al. who focused on the frontal cortex of the brain to determine the concentration of neurotransmitters. Of note however, Alasmari et al did not perform any imaging, unlike Heldt and colleagues. Image analysis was performed on the brains to determine peroxidase-reactive regions which indicates vessel-localized antigens Claudin 5, Occludin, and Glut1; proteins that make up important components of tight junctions. Image analysis also allowed for the total density, branching, and location of microglial cells; macrophages responsible for maintaining the health of the central nervous system by removing damaged neurons. Image analysis of lung tissue created a rendering of total lung area excluding alveolar space. BBB permeability was assessed using 2 tracers and 1 vascular marker injected retro-orbitally just prior to euthanasia. Areas of the brain that were examined were the parietal cortex, caudate nucleus, thalamus, and hippocampus. Leukocyte quantification was done by examining cranial window images of pial vessels at baseline and 2 hours after tumor necrosis factor (TNF) was injected via an

intracerebroventricular cannula located in the right parietal lobe. RNA was extracted from lung tissue, quantified for concentration and purity, then reverse transcripted to DNA to perform a quantitative polymerase chain reaction to determine any fold change expression for intervention groups when compared to the control group. Plasma was collected prior to euthanasia to determine cytokine levels by performing an ELISA test. Affective state and cognitive function were assessed using a novel object recognition test, a Y-maze spontaneous alteration task, an elevated plus maze, and an open field assessment.

In total, approximately 80 male mice, split into 4 unequal groups, were used for this study. Of the 4 groups, 3-10 mice per group were identified for molecular studies and 8-20 mice per group were identified for behavioral analysis. The exact number of mice employed for this study nor the exact number of mice per group were stated. The clinical relevance of this model was determined by comparing body weight and serum cotinine. While all groups at the beginning of the study had comparable weights, the TC group of mice weighed less than all other groups at weeks 2, 4, 6, and 8 with statistical significance occurring at week 4. The researchers found that serum cotinine levels were within a clinically relevant range throughout the duration of the study for the TC and EC1.8% group indicating the successful delivery of nicotine. Following sequencing of micro-vessel mRNA to identify any differentially expressed genes, the researchers found that exposure to the EC0% resulted in a 5.5% increase in upregulated genes and 5.8% in downregulated genes. The EC1.8% group had 0.8% upregulated and 2.2% downregulated while the TC group had 1.4% upregulated and 1% downregulated. The genetic up and down regulation and the relevance to the BBB is specific to Metadherin (Mtdh), Occludin (Ocln), monocarboxylate transporter 1 (Slc16a1), Glut1, an inflammation associated transcripts like Cxcl12, Ifnar1, and integrin alpha 4 (Itga4). Mtdh is important for tight junction maturation

and overexpression may result in downregulation of excitatory amino acid transporters. Mtdh was found to be increased in the EC0% group with no differences in the EC1.8% group and TC group. Ocln, an important protein in the development of tight junctions was significantly reduced in the EC0% group with upward trends in the EC1.8% and TC groups. Slc16a1 is an important transporter of lactate, pyruvate, and branched chain amino acids and is upregulated by all 3 groups with statistical significance occurring for both EC groups but not the TC group. Glut1 is the sole glucose transporter for the BBB. The impact of EC0% caused a decrease in expression of Glut1, an increase in expression following exposure to TC, and no changes observed after exposure to EC1.8% in micro-vessels. However, in the parietal cortex, expression of Glut1 is decreased across all 3 groups when compared to the control group with statistical significance occurring in all 3 groups. Regarding the upregulation of inflammatory associated transcripts, TC exposure caused increases in expression of Cxcl12 and Ifnar1 while EC1.8% showed increases in expression of Itga4. Expression of tight junction proteins Occludin and Claudin 5 were significantly decreased in the cortex of all 3 groups when compared to the control group. While there is a downward trend in expression of these tight junction proteins in the basal ganglia, none of the groups achieved statistical significance when compared to the control group. In order to observe changes in the permeability of the BBB, 2 tracers (NaF and TMR-Dextran) were used to directly observe any changes to tight junctions. In the EC0% group, tracer deposition, indicative of permeability, was increased across all regions of the caudate, thalamus, hippocampus, and the cortex with the majority of permeability occurring in the medial structures of the hippocampus and the thalamus with statistical significance observed in the latter structure. Tracer deposition had a downward trend in the EC1.8% group and no conclusive effects were noted in the TC group. The BBB is a boundary between the CNS specific immune system and the peripheral

immune system. The scale to which the leukocyte interaction occurs at the BBB is an indicator of permeability. Prior to injection of TNF, no leukocytes were observed regardless of group. Following TNF injection, leukocyte counts were increased in all 3 groups when compared to the control group. The EC0% group had significantly more leukocytes when compared to the EC1.8% and TC groups with the TC group being greater than the EC1.8% group. Image analysis of the pulmonary bronchioles and vasculature revealed an increase in the number of macrophages surrounding the bronchioles and vasculature of the EC1.8% exposed mice when compared to the control, EC0%, and the TC groups. Blood plasma measurements of proinflammatory cytokines were performed on all groups with all cytokines measuring unchanged or below the lower limits of detection. The number of microglial cells in the parenchyma of the basal ganglia is increased only in the EC1.8% group indicating potential neuroinflammatory changes. The results of the behavioral analysis yielded no differences between any of the groups with respect to spontaneous exploratory behavior or control over movement. Short-term memory performance was impaired in the EC0% group when compared to the EC1.8%, TC, and control groups. The greatest anxiolytic effects were noted in the TC group when compared to the control and EC1.8% groups.

The limitations of this study are similar to Alasmari et al in that this animal study contained a small sample size and used only male mice, and because of this, the results are difficult to generalize to other species. The potential gender difference also limited the findings related to the intervention. Another similar limitation to Alasmari et al is the controlled conditions which does not correlate to real life EC use as well as the translation of animal studies over to human studies.

Ocular

The third article included in this literature review was published by Md Isa et al[21] in 2019 and sought to determine the effect of long-term vaping on ocular surface health. Different from Alasmari et al and Heldt et al, this study is a cross-sectional, single-visit, pilot design that recruited human participants rather than utilizing mice. This study recruited participants that were between the ages of 19 and 30 years old that could be divided into an intervention group of EC users and a control group of nonsmokers. Inclusion criteria for the intervention group was at least 1 year of vaping history with daily use of at least 3ml per day of EC liquid that contained a composition of at least 50% propylene glycol. The composition of EC liquid used in this study is similar to Alasmari et al whose protocol utilized an EC liquid with a composition of 50% propylene glycol and 50% vegetable glycerin. Exclusion criteria included individuals who wore contact lenses, recently used artificial tears or eye drops, known dry eye or other ocular disease, had laser keratomileusis or refractive surgery, and heavy dual EC and TC smokers. In order to avoid variation, all data was collected during the hours of 2 pm and 4 pm. Participants answered questionnaires to determine their demographic status and vaping profile, including device voltage, followed by the Ocular Surface Disease Index questionnaire to establish dry eye symptoms. The scores had a range from 0 to 100 points where a score from 0-12 indicated a normal ocular surface, 13-22 indicated mild, 23-32 indicated moderate, and 33-100 indicated severe ocular surface disease. The assessment of the cornea and tear film began with least invasive examination and ended with the most invasive to minimize reflex tears with both eyes being utilized for all measurements. The noninvasive tear breakup time was used to measure tear film stability by recording the time it took for an ophthalmometer to measure anterior corneal curvature changes after participants performed full blinking. Researchers recorded 5-time

intervals with the average of the 3 closest values used as the tear breakup time. Fluorescein breakup time was used to measure tear film stability by gently mixing fluorescein into each participant's tear film and asking them to then blink while viewing the ocular surface with a slit-lamp. The breakup time was recorded as the time it took for the first dark spot to appear after blinking. Researchers took 3 measurements and calculated the average as the fluorescein break up time. The National Eye Institute corneal grading system was used to grade any corneal staining. Tear meniscus height was determined using image analysis to calculate tear volume and no additional fluorescein was added to avoid overestimation and reflex tearing. Researchers took 3 measurements and calculated the average. The Schirmer test was performed with a series of 5-minute intervals between irrigation of previous fluorescein dye, instillation of 0.5% proparacaine hydrochloride for topical anesthesia, and then placement of the folded Tear Touch Schirmer's Strip into the lower conjunctival sac of both closed eyes where the length of wetted strip was recorded.

This study utilized 42 total participants, all male, split into 2 equal groups containing 21 individuals in the EC group and 21 individuals in the nonsmoker group. In the EC group, 6 participants stated their EC power output was 3.0-3.9 volts, 9 participants stated their EC power output was 4.0-4.9 volts, and 6 participants stated their EC power output was 5.0-5.9. The average age of participants was 22 ± 2 years. Researchers utilized a survey to determine that the EC group's vaping history was approximately 17.2 months ± 6.5 months, and the frequency of daily vaping sessions was 4 times per day ± 2 times. The results of the Ocular Surface Disease Index questionnaire showed that the EC group experienced moderate to severe dry eye. When examining the results of the questionnaire compared to EC device power output, participants with device voltage of 5.0-5.9 volts experienced significantly higher scores on the Ocular

Surface Disease Index questionnaire, an average score of 44.8, indicating severe dry eyes. The participants in the 3.0-3.9v and 4.0-4.9v groups, with an average score of 14.6 for both groups but both experiencing a wide range, experienced mild to moderate dry eye. The noninvasive tear breakup time and fluorescin break up time indicated that the tear film stability in the EC group was significantly decreased. For the nonsmoking group, the average noninvasive tear breakup time was 6.57 seconds while the EC group was approximately 3.13 seconds. When examining device power output, those individuals in the 5.0-5.9v group experienced the lowest average noninvasive tear break up time at 2.02 seconds, followed by the 4.0-4.9v group with 3.14 seconds, and finally the 3.0-3.9v group with 3.95 seconds. For the nonsmoking group, the average fluorescein break-up time was 4.12 seconds while the EC group was approximately 2.68 seconds. When comparing the average fluorescein break up time across the varying voltage groups, the 5.0-5.9 group experienced 2.02 seconds, followed by the 4.0-4.9v group at 3.14 seconds, and finally the 3.0-3.9v group at 3.95 seconds. The tear volume, indicated by tear meniscus height, was significantly reduced in the EC group, with the average height in micrometers (µm) for the EC group at 203µm and for the nonsmoker group at 235µm. When comparing device power, the 5.0-5.9v group had the lowest tear meniscus at 197.5µm, followed by the 4.0-4.9v group at 201µm, and finally the 3.0-3.9v group at 206.5µm. Results of the Schirmer test showed that a significantly higher production of tears occurred in the EC group than the nonsmoker group. The wetted strip was measured at 14.5mm for the EC group and 8.0mm for the nonsmoker group. When comparing the device power output, the wetted strip was 16.5mm for the 5.0-5.9v group, 14.5mm for the 4.0-4.9 group, and 11.5mm for the 3.0-3.9 group. When examining the significance among the power output groups, all clinical parameters were found to have significant differences except for the difference in tear meniscus height. Of

note, grade 1 corneal staining was noted in 10 participants of the EC group and 4 participants of the nonsmoker group.

The limitations of this study were that the sample size is small, and the entire study was composed of male participants. This is similar to both Alasmari et al and Heldt et al who both had small sample sizes containing only male participants; however, this study differs from both of these in that human subjects are used. The small sample size of this study may limit the effects of the results meaning that if the sample size were larger, the observed effect of the intervention might not be as robust. Additionally, the exclusive use of male participants from Malysia limits the potential findings that are applicable to female participants as well as participants from various ethnic or racial backgrounds.

The fourth article was published by Munsamy et al[56] in 2019 and attempted to determine what effects ECs had on corneal epithelium. Unlike Md Isa et al who performed a cross-sectional, single-visit, pilot study, Munsamy and colleagues designed their study to be a quasi-experimental one group pretest posttest design. This study design is similar to both Alasmari et al and Heldt et al, who performed quasi-experimental studies using mice, which differs from Munsamy and colleagues in their recruitment of human subjects. While Alasmari et al, Heldt et al, and Md Isa et al, focused on the chronic effects of ECs have on various aspects of the neurological and ocular organ systems, Munsamy et al centers more on the acute effects ECs have on the ocular surface of the eye in human participants who were at least 18 years of age. This study recruited participants where exclusion criteria involved participants with acute or chronic systemic disease, history or presence of corneal diseases, ocular or systemic medications, recreational drug users, contact lens users, or individuals who had undergone corneal surgery. This study determined the effect of vaping on corneal epithelial thickness by using a device

called Optovue iVue optical coherence tomographic pachymetry to generate a corneal scan and pachymetry map that showed corneal epithelial thickness divided by region (central, superior, inferior, nasal, and temporal). This differs from Md Isa et al who focused solely on tear film stability; however, Munsamy et al included several tear film stability tests, though their methods were different from Md Isa et al. Unlike Md Isa and colleagues who used fluorescein break-up times, tear height, and the Schirmer test to determine tear film stability, Munsamy et al utilized the Non-Invasive Keratography Break-up Time (NIKBUT) with the Oculus keratography 5M. This method is a simple, noninvasive screening test that provides information about tear break-up over time including a map showing the size and location of the tear break-up region. Following data collection, the average tear film break-up time of all regions were calculated and assigned a stability level of 0, 1, or 2. Level 0 represented stable tear film lasting 14 seconds or longer, level 1 represented critical tear film that lasted longer than 7 seconds but less than 14 seconds, and level 2 represented unstable tear film that lasted less than 7 seconds. Each participant was required to vape 10 puffs of EC liquid that contained 8mg/ml of nicotine. The components in the EC liquid, other than the concentration of nicotine, were not disclosed. Prior to and following each vaping session, participants underwent epithelial pachymetry and NIKBUT measurements to obtain pre and post-test measurements.

There was a total of 64 participants, 43 males and 21 females, who were admitted into this study. Of the 64 individuals, 58 had reliable pachymetry scans for corneal thickness measurements and 57 participants had reliable NIKBUT data from scans. Of note, information regarding the age of the participants was not disclosed. The corneal epithelial thickness analysis was split into regions; central, superior, inferior, nasal, and temporal. All of these regions measured increasing thickness changes post-EC use; however, the changes were not statistically

significant. When comparing the NIKBUT data from pre-EC use to post-EC use, the average tear breakup time changed from 12.72 seconds to 14.12 seconds. This change was shown to be statistically insignificant with 41.1% of participants with stable NIKBUT readings, 42.8% with moderately unstable NIKBUT readings, and 16.1% with unstable NIKBUT readings post-EC use. These findings are in opposition to what Md Isa et al. found; statistically significant decreases in tear breakup times in their study.

The limitations of this study are that the sample size is limited, there was a lack of access to exclusive EC users, the inclusion of EC naïve subjects, and the influence on corneal surface changes. Similar to Alasmari et al, Heldt et al, and Md Isa et al, the sample size was a limitation to this study and might yield different results should a larger sample size be utilized. This study sought to use participants who exclusively used ECs which proved to be difficult during recruiting. This was a limitation in that it could impact the ability to accurately represent the results obtained. Another limitation was in recruiting individuals who had never used an EC before, which could have influenced the results of the study based on the ability of these individuals to learn how to use the device. Finally, the amount of EC liquid vaped is a limitation because it may not have been a significant amount of vapor to cause observable changes to the corneal surface.

Oropharyngeal

The fifth article by Schwarzmeier et al[57] was published in 2021 and investigated the potential cyogenetic and cytotoxic damage based on the evaluation of micronuclei and metanuclear anomaly frequency in the oral mucosa of EC users versus TC smokers versus former TC smokers and a control group of nonsmokers. This is the first study examined in this review that compares former smokers to current TC and EC users. Similar to Alasmari et al,

Heldt et al, and Md Isa et al, a control group was utilized to provide comparison. The study design is quasi experimental with human participants, much like Munsamy and colleagues. The inclusion criteria for this study were the absence of any history of malignancy or visible clinical signs of change in the oral cavity. The exclusion criteria were consumption of other forms of tobacco that were not TC, alterations noted to the oral mucosa, and any previous cancer treatment including, but not limited to, surgery, radiotherapy, or chemotherapy. Schwarzmeier and colleagues recruited and split participants into 4 groups for this study. The EC group was composed of users with a history of at least 5 months of EC use where each participant's use was quantified as EC liquid consumption in mLs/day and concentration of nicotine in mg to determine dependence level and dose effect. This is unlike all previously reviewed articles in that the consumption of EC liquid was made constant, like in Alasmari et al, Heldt et al, and Munsamy et al, or to meet the participation requirement, a minimum consumption amount was defined, like Md Isa et al. The smoker group was composed of users that were attending the Outpatient Smoking Cessation Program of the Heart Institute at the University of Sao Paulo, and like the EC group, each participant's use was quantified by determining the number of cigarettes per day, years of use, calculated smoking load, and carbon monoxide concentration in exhaled breaths. The former smoker group was composed of participants undergoing smoking treatment with abstinence for at least 1 year and a maximum of 2 years attending the Outpatient Smoking Treatment Program of The Heart Institute at The University of Sao Paulo where this group's past use was quantified in the same way that the smoker group was. The control group were current nonsmokers and not defined as never smokers. Researchers determined nicotine dependence by using the Issa Situational Consumption Score which generated a score between 0 and 4 that described nicotine dependence with the lower score indicating low dependence and the higher

score indicating high dependence. The quantification of smoking load was determined by calculating pack years. Next, researchers evaluated CO concentration of exhaled air and plasma cotinine to evaluate cigarette and nicotine consumption. Of note, the information obtained regarding the former smoker group relied on medical records following smoking cessation. Researchers then performed exfoliative cytology of the lateral border of the tongue and mouth floor by using a cytobrush for the collection of material and then affixing the treated and collected material to slides for microscopic examination. Slides were examined under 400x and 1000x magnification in order to properly detect and evaluate micronuclei, with each sample containing approximately 1500 cells for examination. Micronuclei are the result of nucleus fragmentation during cell division that are important to evaluate when structural or numerical chromosomal aberrations occur. Analysis of slides consisted of evaluating the number of cells with 1 micronucleus, more than 1 micronucleus, total micro-nucleated cells, and total micronuclei. The metanuclear anomalies that were evaluated were karyolysis, karyorrhexis, binucleation, the presence of broken eggs, and nuclear budding. Metanuclear anomalies like binucleation, broken eggs, and nuclear buds can show defects in cytokinesis and chromosomal instability or DNA damage while karyolysis and karyorrhexis are anomalies that are associated with cell death.

The total number of participants for this study was 91 individuals, 50 males and 41 females, with the EC user group containing 20, the smoker group containing 22, the former smoker group containing 22, and the non-smoker or control group containing 27 individuals. The average age of the EC user group and the smoker group was 41 years with ages ranging from 17 to 60 years and 51 years with ages ranging from 29 to 70 years, respectively. The former smoker group and control group of nonsmokers had an average age of 58 years with ages ranging from

38 to 73 years and 56 years with ages ranging from 30 to 80 years, respectively. In addition to sex and age, other profile categories included in this study were education level, alcohol consumption, and typical daily doses of alcohol consumption. The average EC use history was, on average, 31 months with the range being 5 to 96 months. Of note, 18 out of the 20 individuals in the EC user group, were former TC smokers. The measured plasma cotinine levels varied from less than 25 nanograms (ng) to greater than 200ng for EC users. There were 3 individuals with plasma cotinine levels that were less than 25ng/mL who claimed to have consumed between 4-5mL/day of EC liquid that contained either 0mg of nicotine or 18mg of nicotine. There was 1 individual with plasma cotinine levels that were 25-40ng/mL who claimed to have consumed an unknown amount of EC liquid per day that contained 6mg of nicotine. There was 1 individual with plasma cotinine levels that were 41-99ng/mL who claimed to have consumed 12mL/day of EC liquid that contained 1.2mg of nicotine. There were 7 individuals with plasma cotinine levels of greater than 200ng/mL who claimed to have consumed either 5mL, 10mL, or 30mL per day of EC liquid that contained 2mg or 4mg of nicotine. The average number of cigarettes consumed was determined using a questionnaire and review of medical records with the EC user group, prior to the use of ECs, consumed on average 23 TCs per day. The smoker group and former smoker group, on average, consumed 17 and 18 TCs per day, respectively. Smoking load, or pack years, was determined for all 3 groups with the EC group and the smoker group achieving approximately the same amount at 29 pack years while the former smoker group achieved 37 pack years. Nicotine dependence level was determined using the Issa Situational Consumption Score where average dependence scores for the EC group were 2, the average smoker group scores were 2.86, and the average former smoker scores were 2.91. The evaluation of exhaled CO in parts per million (ppm) was another way TC consumption was measured with former

smokers measuring at 1.7ppm, EC users measuring at 4.58ppm, and TC users measuring at 10.14ppm. Evaluation of cells with only 1 micronucleus showed a significant increase in the smoker group, followed by the EC group, then the former smoker group, with the control group displaying no cells with 1 micronucleus. Evaluation of total micro-nucleated cells showed a significant increase in the smoker group, followed by the EC group, then the former smoker group with the control group displaying no micro-nucleated cells. Evaluation of the number of micronuclei showed significance in the results with the smoker group having the most, the EC group having the second most, followed by the former smoker group, and the control group with no cells containing micronuclei. The results for the groups containing cells with karyolysis, karyorrhexis, binucleation, the presence of broken eggs, and nuclear budding were significant. The frequency of karyolysis was found to be highest in the EC group followed by the smoker group with former smokers and the control group obtaining low rates of equal value. The frequency of karyorrhexis was highest among the smoking group, followed by the EC group, then the former smoker group, and finally the control group with no observed karyorrhexis. The presence of binucleation, presence of broken eggs, and nuclear budding showed the EC user group with the highest frequency for all 3 categories. For the binucleation category, the former smoker group followed closely behind the EC group, then the smoker group, and finally the control group. For both the categories of broken eggs and nuclear budding, the smoker group had the second highest frequency with the former smoker group and the control group having no observed broken eggs or nuclear budding. It should be noted that the sample area containing the highest significant abnormalities was the tongue.

The limitations of this article are that there is missing data in medical records, there was difficulty in standardizing the concentrations of EC liquid used, there was no scale for nicotine

dependence, and there was a high incidence of alcohol use among participants. The missing data in medical records is a limitation of this study because it yields incomplete and inaccurate data for analysis. The inability to standardize the concentrations of EC liquid could lead to variability in exposure level and create erroneous results. The lack of a scale for nicotine dependence is a limitation because the correlation between the effects on oral mucosa cells and EC use is an important aspect of this study. Finally, the high incidence of alcohol use among participants could influence the results of this study and make it difficult to determine that the effects seen are from the use of ECs alone.

The sixth article, published by Tommasi et al[58] in 2019 explored the effects of exclusive EC use and exclusive TC use on gene regulation by examining the oral transcriptome in these two groups when compared to nonsmokers. This is similar to Heldt et al and Schwarzmeier et al who compared their intervention groups of TC smokers and EC users to a control group of nonsmokers. However, a major difference in these 3 studies is that Heldt et al utilized non-nicotine containing EC use in their study while Schwarzmeier et al included former smokers in their study. Unique to the quasi-experimental study designs of Alasmari et al, Heldt et al, Munsamy et al, and Schwarzmeier et al, this quasi-experimental design was intentionally blinded in order to decrease the risk for bias. Additionally, sample collection and processing of the collected samples from different groups were done in variable orders and not batches in order to blind the researchers from bias. Unlike all of the other studies, who described inclusion and exclusion criteria, Tommasi and colleagues performed a dual phone and in-person screening questionnaire to confirm eligibility. Inclusion criteria specifically defined in this study were that eligible candidates were of both sexes and of diverse races and ethnicities. Exclusion criteria for participation was any indication of oral infection, inflammation, gum disease, dental decay, any

disorder of the immune, pulmonary, or kidney systems, diabetes, BMI that was less than 18kg/m2 or greater than 40kg/m2, any unstable or significant medical conditions that had occurred in the last 12 months, being pregnant or having given birth in the last 12 months, any history of uncontrolled mental illness or substance abuse, and use of any medication that caused induction or inhibition of CYP450 2A6 enzyme. The 3 groups were exclusive EC users, exclusive TC smokers, and a control group who were nonsmokers and non-vapers. EC users had to report exclusive and current use of ECs at least 3 times per week for a minimum of 6 months. Composition of EC liquid nor nicotine concentration was defined for participants. TC users had to report exclusive and current use of TC at least 3 times per week for a minimum of 1 year. The nonsmoker, non-vaper control group were those participants who reported no use of any tobacco product more than 5 times in their lifetime and with no use occurring within the past 6 months. All participants were asked to refrain from eating, smoking, or using an EC for at least 1 hour prior to samples being taken and in addition, were asked to rinse their mouths with water to remove any saliva, food particles, or mucosal debris. Using sufficient pressure and a rotatory motion, an ultrasoft Oral-B toothbrush was used on the interior surface of each participants bilateral cheeks. The proximal, central, and distal regions of the inside surface of each participant's bilateral cheeks were brushed 15 times. This is a different collection method and location than Schwarzmeier and colleagues who used a cytobrush for collecting oral cells from the tongue and mouth floor. Total RNA was isolated, processed, and analyzed using the Database for Annotation, Visualization, and Integrated Discovery Bioinformatics Tool. RNA was reverse transcripted to determine the expression level of individual up-regulated and down-regulated genes. This is different from Schwarzmeier et al who used a microscope to analyze cellular structures at varying magnifications to correlate genetic damage to each group. Both

plasma cotinine and exhaled CO levels were measured to determine smoking status and consumption, similar to Schwarzmeier et al. However, in addition to these measurements, the percentage of carboxyhemoglobin was also calculated for this study to evaluate cigarette and nicotine consumption.

Ninety-three participants were recruited for this study with the EC user group containing 42, the TC group containing 24, and the control group of nonsmokers containing 27 individuals. A total of 69 males and 24 females were a part of this study with representation from various races, educational backgrounds, marital status's, employment status's, annual incomes, and BMIs included in the population characteristics. This study shows some similarities to Schwarzmeier et al. in their inclusion of additional factors in their population analysis of educational background and alcohol consumption. In order to attempt to quantify smoking or vaping status, plasma cotinine was drawn and shown to be significantly higher in both the EC user and smoker groups than nonsmokers. CO in exhaled breath and percentage of carboxyhemoglobin was shown to be significantly higher in the TC group than both the EC and control groups. An analysis was performed on the total amount of genes that were differentially expressed with significant increases, over 1.5 times greater, noted in both the EC and TC group compared to the control group. Of note, the TC group had nearly 50% more abnormal gene expression than the EC group. While the TC group had 1383 upregulated and 343 downregulated genes, the EC group had 857 upregulated and 295 downregulated genes. Researchers then further explored the differentially expressed genes by creating a list of the top diseases and biochemical pathways associated with their downstream targets. For the EC user group, the top 5 disease processes related to genetic changes, in order from greatest to least were: cancer, organ-related injury or abnormality, neurological diseases, psychological diseases, and gastrointestinal

disorders. For the smoker group, the top 5 disease processes related to genetic changes, in order from greatest to least were: cancer, organ related injury or abnormality, gastrointestinal disorders, dermatological conditions, and infectious diseases. For the EC group, the top 5 biochemical pathways that were affected, in order from greatest to least were: Wnt/Ca2+ pathway, the protein ubiquitination pathway, aryl hydrocarbon receptor signaling, tRNA charging, and aldosterone signaling in epithelial cells. For the smoker group, the top 5 biochemical pathways that were affected, in order from greatest to least were: integrin signaling, phagosome maturation, insulin receptor signaling, ERK/MAPK signaling, and actin nucleation by ARP-WASP complex. Utilization of the Database for Annotation, Visualization, and Integrated Discovery Bioinformatics Tool identified the categories of functional genes most affected in the EC user group were those involved with chaperones, the stress response, ATP-binding, and tumorigenesis with emphasis on smoking-related cancers like lung cancer, squamous cell carcinoma of the head and neck, esophageal cancer, bladder cancer, ovarian cancer, and leukemia. The categories of functional genes most affected in the smoker group were those involved in keratinocyte differentiation, small GTPase superfamily, cell-cell adhesion, and protein serine/threonine phosphatase activity.

The limitations of this study were that the sample size and composition were small, the exclusivity of EC versus TC versus nonsmoker groups, reliance of self-reported social habits, and variability in EC products. The limitations of this study were similar to Alasmari et al, Heldt et al, Md Isa et al, and Munsamy et al in that the sample size was small and the age distribution was limited, which may yield results that would not be repeatable with a larger sample size. The exclusivity of each group of participants was a limitation in that it did not account for individuals who use both EC and TC, which was not only a large population of individuals but may not

accurately represent a real-life setting. The reliance this study has on self-reporting each participant's vaping or smoking status is a limitation that may result in inaccurate reporting of use. The variability in EC products is a limitation in that the amount of inconsistency that is reflected in the results is unknown due to consumption levels.

Pulmonary

The seventh article, published in 2018 by Coppeta et al,[59] assessed whether the active use of ECs by healthy subjects can cause short term changes in lung function and whether these changes are similar or different to TC smokers. A secondary aim of this study was to determine the impact of ECs and TCs on environmental pollution by examining the concentration of particles in confined space over time. The research design is comparable to Alasmari et al, Heldt et al, Munsamy et al, and Schwarzmeier et al in that a quasi-experimental design is utilized. However, unlike all of the previously mentioned studies, Coppeta et al. also employed a cross-over design. Human participants were recruited for this study, like all previously mentioned studies aside from Alasmari et al and Heldt et al, who used mice. This study was unique in that it recruited only healthy nonsmokers who excluded if they had 1 or more of the following conditions: chronic bronchopulmonary diseases in the acute phase, respiratory allergies or symptoms, acute or chronic disease affecting the cardiovascular, hepatic, renal, or immune systems. Participants were also excluded if they could not perform spirometric tests such as with pregnancy, recent abdominal surgery, thoracic or ocular episodes of hemoptysis, myocardial infarction within 3 months or unstable angina, thoracic aneurysm, pneumothorax, oral pain exacerbated from the spirometric mouthpiece, dental implants, dementia or confusion, and language difficulties. Also excluded were those participants who were ex-smokers and those who reported previous spirometric changes related to drugs acting on the pulmonary tract.

Participants were asked to avoid alcohol up to 4 hours prior to testing and to abstain from heavy physical activity or eating up to 2 hours prior to testing. Similar to Munsamy et al, the researchers sought to determine the acute, rather than the chronic, effects of EC use. Each participant, on different days, partook in a 5-minute smoking session of either an EC or a TC. While there was no defined washout period for this study, it is noted that at least these sessions occurred on different days. The EC used for this study is the EGO P (L) with a manual start that contained EC liquid comprising of 18mg/ml of nicotine, propylene glycol, glycerol, vegetable flavorings, and deionized water in the brand Latakia tobacco aroma. Though the ingredients of the EC liquid were provided, the exact concentration of these components were not included. The TC had a composition equal to 0.6mg of nicotine, 8mg of tar, and 9mg of CO. Participants were asked to smoke the EC or TC over a 5-minute period, performing 15 puffs total, different from Munsamy et al, who specified 10 puffs in their protocol. Prior to lung function testing, height and weight was obtained from each participant along with a full ventilatory inspiratory and expiratory maneuvers. During each day, 3 spirometric evaluations were performed: before smoking (baseline), within 1 minute of smoking, and 15 minutes after completion of smoking. The use of a flow-based spirometer was used to obtain the following measurements for 3 consecutive trials: Forced Vital Capacity (FVC), forced expiratory volume in the first second (FEV1), FEV1/FVC, Peak Expiratory Flow (PEF), forced expiratory flow at 25% of FVC (FEF 25%), forced expiratory flow at 50% of FVC (FEF 50%), forced expiratory flow at 75% of FVC (FEF 75%), and forced expiratory flow between 25% and 75% of FVC (FEF 25-75%). Results were expressed as the onset of obstruction, changes in the FEV1/FVC ration, changes in FEV1, or changes in FEF 25-75%. Obstruction was diagnosed in subjects with FEV1/VC below the lower limits of normal or in subjects showing a change in FEV1 > 20% compared to baseline.

The environmental impact of EC and TC use was measured using emission assessment of nanoparticles using 2 different devices: the Optical Particle Counter (OPC) and the Condensation Particle Counter (CPC). The OPC measured the concentration of airborne dust with a micron sensitivity of 0.3 microns to 10 millimicrons. The CPC measured the concentration of airborne dust every second and can detect particles smaller than 1 micron and can provide guidance on the presence of nanoparticles. The environmental impact measurements were performed at baseline, during active smoking of ECs and TCs individually and for 60 minutes after each independent smoking session.

A total of 30 never smokers, 17 men and 13 women, were enrolled for this study. The average age was 32 years and the average BMI 23.2. A significant decrease in FEV1 for the TC group, when compared to baseline, was observed after the cessation of smoking at 1 minute and at 15 minutes. The FEV1 was significantly decreased for the EC group, when compared to baseline, at 1 minute after vaping but not at 15 minutes after vaping. The FEV1/FVC and FEF 25-75% were significantly reduced from baseline at 1 minute and 15 minutes following TC smoking. A significant decrease in FEV1/FVC ratio and FEF 25-75% for the EC group after 1 minute with a persistent decrease at the 15-minute mark for FEF 25-75% but not in FEV1/FVC ratio. During and after the TC smoking session, the average concentration of particles in the room was 42,645pp/cm3 with a range of approximately 2,310-500,000pp/cm3. During and after the EC vaping session, the average concentration of particles in the room was 49,690pp/cm3 with a range of 5040-500,000pp/cm3. The concentration of particles dropped to baseline in the EC room after 5 minutes and after 30 minutes in the TC room.

The limitations of this study were that there was a small sample size, a short duration of exposure with results examined for acute measurements, the lack of a control group, and the

variability of ECs and TCs used. The small sample size was similar to all previously stated articles other than Schwarzmeier et al. The small sample size was a limitation because it could impact statistical power and repeatability of results to a larger population. The 5-minute exposure per session was a limitation because it may not accurately represent the typical pattern of individuals who smoke or vape, which will alter the accuracy of the results. The lack of a control group was a limitation due to the lack of comparison or baseline measurements to evaluate the groups. The variability in product use can affect the ability of the study to generalize the results to different products.

The eighth article by Song et al[60] was published in 2020 and focused on examining acute lung inflammation and gene expression of healthy individuals when nicotine free and nicotine containing ECs are used. This is similar to Heldt et al who also investigated the effects of non-nicotine containing ECs as one of their intervention groups. This study recruited human participants, much like all of the aforementioned studies other than Alasmari et al. and Heldt et al. Additionally, Song and colleagues recruited healthy, never smokers to participate in this study, similar to Coppeta et al. This means that no control group was used for comparison for this study, much like Munsamy et al and Coppeta et al. Recruitment was done using advertisements followed by a phone screening to confirm eligibility. Participants were aged 21-30 years and were excluded if they had a history of significant medical problems including lung disease, general anesthesia or bronchoscopy within the previous year, recent drug use, BMI > 40, use of other combustible tobacco within the past year, pregnancy, or any other medical disorder that would affect their bronchoscopy risk. Unlike all other previously discussed articles in this literature review, Song et al was the first to perform a randomized controlled trial. In this study, participants, the site of bronchial alveolar lavage, and bronchial brushing locations were

randomized to avoid bias among researchers. This showed some similarities to Tomassi and colleagues who performed a blinded quasi-experimental study where their sample collection and processing of samples was blinded to remove bias. Baseline bronchoscopy was performed on all participants where samples were collected by bronchial alveolar lavage for inflammatory cells and cytokines and bronchial brushings were collected from normal appearing epithelium for gene expression assays. Participants were provided with an EC 1 week after the baseline bronchoscopy was performed and trained on how to use the device. The EC was an Innokin iTaste VV 4.0 refillable tank device with flavorless EC liquid that contained 50% propylene glycol and 50% vegetable glycerin without nicotine. Participants in the intervention group were instructed to use the device at least twice per day over 60 minutes each time, performing 20 puffs. This was unique from other previous described studies where Munsamy et al utilized 10 puffs and Coppeta et al utilized 15 puffs. The device chosen for this study conveniently included an LED screen that counted the number of puffs taken. Participants received daily reminders via text message to use the EC device and were required to send a photo displaying the puff counts to ensure compliance with protocol. After 2 weeks of use, the intervention group was evaluated in person for compliance or any adverse events. After 4 weeks of EC use, all participants underwent a second bronchoscopy, 5 weeks after the baseline bronchoscopy, where samples were taken from the opposite side of the baseline samples. Both baseline and secondary bronchoscopies were performed under light intravenous sedation. Urine was collected at the time of the second bronchoscopy. Unlike all of the previously discussed studies, the participants in this study were financially compensated for their participation; $37 for the orientation visit and $200 for each bronchoscopy. Assays that were done for data collection included bronchial alveolar lavage cell counts and determination of inflammatory cytokines like IN-ɣ, IL-1β, IL-2,

IL-4, IL-6, IL-8, IL-10, IL-12p70, IL-13, and TNF-α. This is similar to Heldt et al who also examined plasma cytokines via ELISA. Total RNA was extracted from bronchial brushings to determine any upregulation or down regulation of gene expression. A urine spot test was performed to determine the concentration and presence of propylene glycol.

A total of 30 participants were enrolled in this study. When comparing baseline and post-intervention bronchoscopy samples, there was no statistical significance observed. There were trends showing decreases in average cell concentration, macrophages, lymphocytes, and neutrophils of the EC group with the control group seeing the opposite trend of increasing average cell concentration and macrophages. Urine propylene glycol levels were significantly increased in the intervention group but not the control group. When comparing changes in urinary propylene glycol levels to cell counts and inflammatory cytokines of the intervention group, there was statistical significance for positive correlations with changes in cell concentration and lymphocyte counts. Additionally, changes in several cytokines, IL-8, IL-13, and TNF-α, were found to be significantly correlated with the intervention group but not the control group. There were no significant changes in gene expression from lung epithelial cell brushings.

The limitations of this study were the small sample size, the limited scope of EC liquid product, and the use of self-reporting and compliance. The small sample size, a common theme among all of the articles aside from Schwarzmeier et al, was a limitation in that the results might be different if a larger sample size was utilized. The components of the EC liquid studied was a limitation in that the product studied does not represent the full range of products that are available. The use of self-reporting, similar to Tommasi et al, is a limitation of this study in that bias might occur should participants report inaccurate testaments.

Cardiovascular

The ninth article was published in 2019 by Biondi-Zoccai et al[61] who focused on the acute effects of TCs, ECs, and a new generation heat-not-burn cigarette (HNBC) on oxidative stress, flow-mediated dilation of vasculature, platelet function, and blood pressure. Focusing on the acute, rather than the chronic effects of, TCs, ECs, and HNBCs is shared with Munsamy et al, Coppeta et al, and Song et al. Also sharing similarities to this study are Heldt et al, Schwarzmeier et al, Tommasi et al, and Coppeta et al, who utilized TCs as an intervention group to show trends and comparisons among varying methods of nicotine consumption. To add to the parallels noted amongst the articles in this literature review, the absence of a control group is akin to Munsamy et al, Coppeta et al, and Song et al. However, this is the only study in this literature review that compares the effects of the use of a HNBC to TCs and ECs. Of note, the researchers also compared satisfaction levels of each device which is unique to all other beforementioned studies in this review. The design of this study is an independent, randomized cross over study, which is similar to Coppeta et al who utilized the same design but without randomization. Researchers were blinded to the device being used when examining blood samples, endothelial dysfunction data, and cardiovascular parameters to prevent bias. This study recruited human participants, much like all of the aforementioned studies other than Alasmari et al. and Heldt et al. For this study, healthy participants were recruited if they had no acute or chronic organic, metabolic or inflammatory disease, no fever or infection within 3 months, no cardiovascular symptoms, no allergies, normal blood pressure levels and heart rhythms at screening, not pregnant or menstruating, and were on no medications or supplements known to affect or modulate measurement parameters. Participants were first, tutored on how to use each device and then randomly allocated into 6 different cycles of using a single TC, EC, or HNBC.

Like Munsamy et al and Coppeta et al, no control group was utilized in this study. The randomization list was computer generated and participants did not know which group they would be assigned to until each session began. Sessions consisted of either a single Marlboro Gold TC with a mean nicotine content of 0.6mg per cigarette, a total of 9 puffs from a tobacco flavored Blu Pro EC with a mean nicotine content of 0.58mg per 9 puffs, or a single THS2.2 IQOS with Heets HNBC with a mean nicotine content of 0.5mg per stick. None of the aforementioned devices defined the components, other than nicotine concentration, of the TC, EC liquid, or HNBC stick. Blood samples were drawn just before and immediately after the use of each product. Participants eventually used all 3 products with a washout period of 1 week before switching products. Blood was analyzed for markers of oxidative stress, antioxidant reserve, platelet function, and cotinine levels. Serum levels of soluble Nox2-derived peptide, a marker of NADPH oxidase activation, and quantification of 8-iso-PGF2α-III, a class of prostaglandins that reflects lipid peroxidation, were detected via ELISA to determine levels of oxidative stress. Additionally, hydrogen peroxide levels and serum hydrogen peroxide breakdown activity were measured in serum samples to determine levels of oxidative stress by reactive oxygen species. Vitamin E levels and nitric oxide bioavailability were measured in serum to determine antioxidant reserve and ability to counteract reactive oxygen species. Platelet activation was measured by analyzing 2 markers of platelet activation in the serum. Serum cotinine levels were drawn to measure compliance throughout the study. Endothelial dysfunction was recorded as flow mediated dilation of the vasculature that was measured using ultrasound of the brachial artery. All measurements were obtained between 8 and 10 am with the patient resting in the supine position. The brachial artery was imaged at a location 3 to 7cm above the antecubital crease utilizing a 7.5MHz linear array transducer. A sphygmomanometric cuff was

placed on the forearm and inflated 50mmHg above systolic blood pressure to create flow stimulus in the brachial artery. All measurements were made at the end of diastole and expressed as percent change in post stimulus diameter when compared to baseline diameter. Systolic, diastolic, and mean arterial pressures were recorded and analyzed at baseline and after each smoking session. Following each smoking session, a 7-question survey was conducted with each featuring scores from 0, no effect, to 100, maximum effect, describing satisfaction levels.

The total number of participants for this study, after the exclusion of 30 individuals due to unwillingness to refrain from smoking during the required washout period, amounted to 20 subjects, 6 male and 14 female, with an average age of 35 years. Other population characteristics included was BMI, serum cholesterol, hemodynamic values, family history of cardiovascular disease, and pharmacologic therapy with contraceptives, antiepileptics, or thyroid replacement therapy. Plasma cotinine levels were analyzed before and after exposure to all devices to evaluate for compliance with all products increasing cotinine levels significantly from baseline values. Regarding oxidative stress, all 3 devices showed statistically significant increases of soluble Nox2-dervied peptide, hydrogen peroxide, and 8-iso-PGF2α. The order of greatest to least increases was the TC group, followed by the EC group, and then the HNBC group across all 3 categories of oxidative stress. The antioxidant status of participants was determined by baseline and post-intervention vitamin E levels and hydrogen peroxidase levels. Both vitamin E levels and hydrogen peroxidase levels were significantly reduced in both the TC and EC groups following intervention. While no changes were observed in vitamin E levels for the HNBC, a significant reduction in hydrogen peroxidase levels were observed post intervention. The evaluation of platelet activation was determined by a change in concentration of sCD40L and soluble P-selectin. For all 3 devices, there were significant increases in the concentrations of both

markers of platelet activation with the greatest increase in concentration in the TC group, followed by the EC group, and the least amount of increase in the HNBC group. Endothelial dysfunction was evaluated using flow mediated dilation, NO bioavailability, and blood pressure changes. There was a significant decrease in flow mediated dilation for all 3 devices with the greatest percent decrease occurring in the TC group, followed by the EC group, and finally the HNBC group. A significant decrease in NO bioavailability was observed in the TC and EC groups but not in the HNBC group with the greatest decrease occurring in the TC group. Regarding blood pressure parameters, all devices cause statistically significant increases in systolic, diastolic, and mean arterial pressures. The greatest increases were observed in the TC group, followed by the EC group, and lastly in the HNBC group. Of note, biomarkers for oxidative stress, antioxidant status, platelet activation, and endothelial dysfunction returned to baseline prior to repeated exposure to each device. Satisfaction scores indicated a preference for TC first, followed by HNBC, and least desirable was the EC.

The limitations of this study were the small sample size, focus on specific health outcomes, the focus on specific health outcomes, the limited range of products tested the self-reported smoking history, the limited range of products tested, and the controlled nature of the setting. Like all the other articles discussed other than Schwarzmeier et al, the small sample size that involved the recruitment of homogenous nonsmoking White population without overt clinical conditions leads to generalizability. The focus was on acute effects of a single smoking session so it remains unclear whether chronic tobacco users may lead to more persistent vascular changes and biochemical profiles. This study focused on cardiovascular and oxidative stress parameters while other health dimensions such as pulmonary function or carcinogenesis were not evaluated. This study focused on specific brands of products, which may not represent the wide

variety of products available. The controlled nature of this experimental setting does not accurately reflect a real-world environment, which is a similar limitation found in Alasmari et al. and Heldt et al.

The tenth article was published in 2020 by Gonzalez and Cooke[62] who investigated how acute use of the popular EC brand, JUUL, affects arterial pressure and sympathetic neural outflow. Similar to Biondi-Zoccai et al, cardiac parameters were an important outcome of this study but unlike any of the other articles discussed in this literature review, the impact of EC on microneurography was determined. Like Munsamy et al, Coppeta et al, Song et al, and Biondi-Zoccai et al, this study focused on the acute rather than chronic effects of ECs. This study is a randomized cross over design, comparable to Coppeta et al, but most like Biondi-Zoccai and colleagues. Akin to Heldt et al and Song et al, the utilization of non-nicotine EC liquid was used as a comparison to a nicotine containing EC liquid. This study recruited human participants, much like all of the aforementioned studies other than Alasmari et al and Heldt et al. Participants were enrolled in this study if they had no history of autonomic dysfunction, hypertension, respiratory disease, diabetes, tobacco or vaporized nicotine usage, and not taking any prescribed medications were screened for hypertension prior to being admitted into this study. All female participants were tested only during the early-follicular phase of their menstrual cycle and both male and female participants were instructed to abstain from exercise and caffeine for 24 hours prior to testing. Devices used for this study were the JUUL vape pod system and the SMOK FIT Kit vape pod system. The device pods utilized were mango flavored JUUL EC liquid pods that had 30% propylene glycol, 60% vegetable glycerin, and 59mg/ml of nicotine and mango flavored naked EC liquid pods that contained 30% propylene glycol, 60% vegetable glycerin, and 0mg/ml of nicotine. This composition is unique to all previously reviewed articles in that the

components found in the EC liquid of all the other studies remained equal at 50% each of propylene glycol and vegetable glycerin. Additionally, this study utilizes the highest concentration of nicotine at 59mg/ml, with the second highest, Alasmari et al, utilizing an EC liquid containing 24mg/ml concentration of nicotine. Each participant was tested using both devices at random, approximately 1 month apart. This study is similar to Munsamy et al, Coppeta et al, Song et al, and Biondi-Zoccai et al. in that there was no control group used. Participants were placed in a semi recumbent position where heart rate was recorded continuously via a 3-lead electrocardiogram, respiratory rate was continuously measured using a pneumobelt, and beat-to-beat arterial blood pressure was recorded continuously using a noninvasive NOVA finometer. Multifiber efferent sympathetic nerve traffic was recorded from the peroneal nerve muscle fascicles at the popliteal fossa by using a tungsten microelectrode that obtained a mean voltage display of nerve activity. All participants were then allowed at least 5 minutes of nonrecorded rest to confirm hemodynamic and neural stability. Participants breathed in time to a computer display which was set to 15 breaths per minute. A 10-minute baseline was recorded followed by a 10-minute inhalation protocol. This protocol called for participants to inhale once every 30 seconds on the device for a total of 20 inhalations while keeping in time with the computer display. This puff count is similar to Song et al, who also utilized a 20-puff count for their study. After completing the inhalation protocol, a 10-minute recovery period was recorded where participants were asked to report any symptoms. Plasma cotinine levels were measured before the start of the experiment, immediately after the inhalation protocol, and after the recovery period. This was to ensure participants had not been exposed to any nicotine before using the EC as well as quantify nicotine consumption values throughout the experiment.

A total of 15 healthy young adults, 9 males and 6 females, were recruited for this study. Plasma cotinine levels were analyzed before, during, and after exposure to each vaping device to evaluate for compliance with no detectable increases being noted in whole blood cotinine concentrations before, during, and after intervention. Subjective experiences were also recorded with 11 out of 15 participants reporting feelings of light-headedness and/or throat irritation following the use of the nicotine containing JUUL product and no reported symptoms by any participant after the SMOK FIT product. When compared to baseline values, vaping sessions with the nicotine containing JUUL device caused significant changes in all parameters; increased systolic and diastolic blood pressure, increased mean arterial pressure and heart rate, and decreases in muscle sympathetic nerve activity and spontaneous cardiovagal baroreflex sensitivity. These significant changes continued into the recovery phase for all parameters except for spontaneous cardiovagal baroreflex sensitivity, which returned to baseline values during the recovery period. When compared to baseline values, vaping sessions with the non-nicotine containing SMOK FIT product saw increases in systolic and diastolic blood pressure, mean arterial pressure, and muscle sympathetic nerve activity; however, the findings were not found to be significant. There was no change in heart rate for the SMOK FIT product and a decrease in spontaneous cardiovagal baroreflex sensitivity, though it was not found to be significant. During the recovery phase after use of the SMOK FIT non-nicotine containing device, all parameters returned to normal.

The limitations of this study were the sample size and demographics, the specific brand focus, the self-reported experience, the patterns of vaping, the lack of plasma nicotine measurements, and the study suspension. Similar to all other previously discussed articles other than Schwarzmeier et al, the small sample size was not a good representation of the general

population, and an increased sample size may result in changes to the overall results. This study focused on a specific brand of EC, the JUUL, which does not represent the effects other brands of EC may have on study parameters. The bias introduced by self-reporting is a limitation in that the subjective nature of experience varies among individuals. There is a limitation noted on the pattern of vaping described in this study in that it may not represent real-world usage. This coupled with participants who were naïve to the effects of nicotine may not reflect the effects seen in individuals who regularly use ECs. The lack of measurement of plasma nicotine levels is a limitation of this study, as it could have provided more insight into the absorption of nicotine and its relationship to the cardiovascular parameters being studied. Lastly, a limitation of this study is the suspension of enrollment due to concerns over EVALI, which may have impacted the completeness of the data and therefore accuracy of the results.

The eleventh article was published in 2020 by Chaumont et al.[63] and seeks to determine if the short-term cessation of vaping in heavy EC users would clear aerosol deposits from the lungs resulting in recovery of gas exchange along with improvement of biological and clinical cardiorespiratory parameters. Additionally, Chaumont et al. also sought to determine if EC cessation for 5 days could shift serum and urine metabolomes toward a healthier cardiorespiratory profile. This study is a randomized crossover design similar to Coppeta et al. but most like Biondi-Zoccai et al. and Gonzalez and Cooke. Additionally, this study shows similarities to Munsamy et al, Coppeta et al, Song et al, Biondi-Zoccai et al, and Gonzalez and Cooke in that this study focused on the acute rather than chronic effects of ECs. This study recruited human participants, much like all of the aforementioned studies other than Alasmari et al and Heldt et al. Participants who were healthy, former tobacco smokers and exclusively used nicotine containing EC over the past year were recruited and screened prior to enrollment.

Participants were excluded if they used chronic medication or recreational drugs, had acute or chronic illness, past or present symptoms of cardiopulmonary disease, use medications, or had hypertension. Participants were asked to refrain from caffeine, alcohol, and exercise for 48 hours and be fasting for at least 12 hours prior to each experimental session and study period. The device used for this study was a fourth-generation Alien 220 box mod EC set at 60 watts with an EC liquid containing 50% propylene glycol and 50% glycerol. One EC liquid lacked nicotine while the other contained 1.5mg/ml of nicotine. Akin to Heldt et al, Song et al, and Gonzalez and Cooke, the utilization of non-nicotine EC liquid was used as a comparison to a nicotine containing EC liquid. All participants rotated through the protocol at random. The protocol included 3 periods where in 1 period, participants were asked to vape an EC containing nicotine for 5 days and until 2 hours before the experimental session which required them to vape 10 nicotine containing puffs at 60 watts. A second period asked participants to vape a nicotine free EC for 5 days and until 2 hours before the experimental session which required them to vape 10 non-nicotine containing puffs at 60 watts. A third period asked participants to completely stop EC vaping for 5 days before the experimental session and then perform sham-vaping which mimicked actual vaping but with the device turned off. The cessation of EC use in this study is not considered the control group but intervention; therefore, this study shares the lack of a control group with Munsamy et al, Coppeta et al, Song et al, Biondi-Zoccai et al, and Gonzalez and Cooke. Additionally, the protocol requirement of 10 puffs is similar to that seen in the protocol designed by Munsamy et al. Researchers were blinded to experimental sessions to avoid bias. Following experimental sessions, participants rested for 30 minutes and then were placed in the semi-recumbent position for data collection. A PeriFlux system was used to monitor transcutaneous oxygen and carbon dioxide. Continuous monitoring of oxygen saturation, end-

tidal carbon dioxide, respiration rhythm, and heart rate were assessed using the Capnostream-35-monitor. Systolic and diastolic waveforms were obtained using the Finometer Pro, which also was used to calculate the cutaneous vascular conductance. Blood pressure was taken before and immediately following experimental sessions. A PeriFlow system was used to assess skin microcirculatory blood flow. All readings were recorded immediately before experimental sessions, during, and then for 60 minutes after. Lung function tests were performed 3 hours after the experimental sessions and focused on flow volume curves to include forced expiration and inspiration, lung volumes via body plethysmography, and diffusing capacities for carbon monoxide and nitric oxide. Blood was drawn at the beginning of and approximately 1 hour after experimental sessions while urine specimens were collected at the beginning of and approximately 90 minutes after experimental sessions. Serum concentrations of CC16, creatinine, and surfactant protein-D were examined in blood samples while urine was examined for concentrations of retinol binding protein, creatinine, and CC16. CC16 and surfactant levels are indicative of lung inflammation. Protocol compliance was assessed by examining serum nicotine and propylene glycol at baseline, urine cotinine, and fractional concentration of carbon monoxide during expiration.

This study had 30 male participants with an average age of 38 years. They were regular and exclusive EC users with an average consumption of 17mL of EC liquid daily. Plasma cotinine levels were measured at baseline to maintain compliance and establish washout. The researchers found that all baseline urine and plasma cotinine levels were within acceptable levels for the study aside from high serum nicotine levels and urine cotinine levels in 3 nicotine free sessions and 1 stop session. When compared to sham-vaping, both nicotine-containing and nicotine-free vaping groups experienced a significant decrease in transcutaneous oxygen tension

10 minutes following acute vaping sessions. A significant decrease in transcutaneous carbon dioxide tension occurred 40 minutes following acute nicotine containing vaping sessions when compared to sham vaping. When compared to sham vaping, both nicotine containing and nicotine free vaping groups experienced decreases in both oxygen saturation and end tidal carbon dioxide concentration though neither were significant. No changes were noted across all groups when comparing changes in respiratory rate. When comparing oxygen saturation baseline values, the stop session group had lower oxygen saturation than the nicotine containing and nicotine free groups. No changes were noted to transcutaneous oxygen and carbon dioxide tensions, end-tidal carbon dioxide concentrations, respiratory rhythms, skin microcirculatory blood flow, or cutaneous vascular conductance. Significant increases in systolic and diastolic blood pressures were noted acutely and remained elevated, not returning to baseline, throughout the recovery phase in the nicotine containing vape group. There was a significant increase in the heart rate of the nicotine containing vape group with a return to baseline during the recovery phase. While significant increases were noted in the nicotine free vaping group across all 3 hemodynamic parameters acutely, a return to baseline was noted for all parameters during the recovery phase. Sham vaping resulted in increases in both systolic and diastolic blood pressures though the changes were not significant nor were they as drastic as either the nicotine containing or non-nicotine containing groups. Sham vaping resulted in little to no change in heart rate and the little change that did occur, resulted in a decrease in heart rate. When comparing heart rate baseline values, the stop session group had the lowest heart rate compared with the nicotine and non-nicotine containing groups. FEF-25% was significantly higher in the stop sessions when compared with nicotine free sessions. During acute sessions, changes in serum and urine creatinine, changes in serum surfactant protein-D, and changes in urine retinol-binding-protein

did not vary across groups. When comparing baseline serum CC16 concentrations, stop sessions showed significantly higher concentrations when compared with the nicotine and nicotine-free sessions. Baseline urine PG is lower in the stop session group when compared to both vape groups. Baseline urine 3-hydroxyisovalerate and pyruvate were higher in both vape groups when compared to the stop session. Baseline urine trimethylamine oxide, Hippurate, and N-Phenylacetyl-glycine was lower in the nicotine session when compared to the stop session group.

The limitations of this article were sample size and gender exclusivity, previous smoking history, the techniques used to measure parameters, the short study periods, the focus on specific EC liquid components, the lack of control over vaping behavior, self-reporting compliance, and the limited health outcomes. The small sample size and gender exclusivity, similar to Alasmari et al, Heldt et al, and Md Isa et al was a limitation in that it is not an accurate representation of the population and gender differences that might occur in a real-world setting. The participants former TC smoking history is a limitation, even though they had not smoked a TC in over 1 year and were exclusive EC users, this could still represent inaccurate results of EC exclusive users. The techniques used to measure outcome parameters are a limitation because each EC can emit a specific profile of heavy metals, carbonyls, and CO which may explain why the baseline oxygen saturation was higher in the nicotine and non-nicotine containing groups due to absorbance properties. Additionally, CO baseline levels tended to be higher in active vaping sessions suggesting combustion with high-wattage vaping rather than simple vaporization. This study only focused on EC liquid containing varying nicotine levels and PG, not on whether other components, such as flavoring, could have an impact on the results. Vaping conditions during the 5 days prior to experimental sessions was not monitored. Only 5 days of vaping does not mimic real-world setting, nor does it account for variation in exposure. The participants' self-reporting

could lead to bias and variation in the results, similar to Tommasi et al, Song et al, and Gonzalez and Cooke.

Results

According to Alasmari et al,[54] the chronic, daily use of nicotine containing ECs can alter the concentrations of neurotransmitters within the mesocorticolimbic brain regions and lead to addiction to nicotine. The effects on the concentrations of neurotransmitters may be related to nicotine exposure and additional research regarding the other components found in the liquid of the EC are needed to make further conclusions. Alasmari and colleagues[54] found that the chronic and daily use of ECs resulted in changes to concentrations of dopamine, glutamine, and glutamate in the STR and changes to concentrations of glutamine and GABA in the FC with serotonin concentrations remained unchanged in both regions of the brain. Heldt et al[30] found that the long-term use of ECs can have adverse effects on neurovascular health and may contribute to cognitive dysfunction, regardless of nicotine content. Additionally, Heldt et al[55] determined that the effects of ECs may be equivalent to combustible TC and have uniquely damaging properties. More research is needed to further understand the specific components and byproducts which are implicated in these effects to determine the mechanism at which these changes occur.

Following the completion of their study, Md Isa et al[21] found that individuals who use ECs experience moderate to severe eye dryness along with improper tear film stability. However, these individuals also appeared to have an overproduction of tears which is thought to act as a countermeasure to combat the dry eye symptoms. A secondary outcome that Md Isa and colleagues[21] found was that as the EC device increased in power output, so too did the worsening of symptoms experienced by the user. The outcome obtained from the study performed by

Munsamy et al[56] revealed that 10 puffs from an EC resulted in no statistically significant changes to the integrity or thickness of the corneal surface or in the stability of tear film. However, Munsamy and colleagues[56] noted a negative clinical trend with only 10 puffs from an EC, which may be amplified with increases in puff number and repeated vaping throughout the day.

Schwarzmeier et al[57] concluded that the use of EC presented genotoxicity and cytotoxicity in the oral mucosa cells. However, there is a need for further research to delineate the degree of damage that is attributable to the consumption of alcohol. The results obtained from the whole transcriptome analysis performed by Tommasi et al[58] found that individuals who were exclusive EC users have deregulation of key genes, similar to TC smokers, the majority of which converge on cancer-related pathways. Tommasi et al[58] also determined that future research should target the long-term effects of EC use along with the effects associated with the passive exposure to vapor from ECs.

The results obtained from Coppeta et al[59] regarding the use of ECs in healthy participants yielded worsening of ventilatory function after only 5 minutes of exposure mimicking an obstructive like disease process. While Coppeta and colleagues[59] found that these negative outcomes were not as severe as those seen in participants exposed to TC smoke, they maintained significance. In addition, Coppeta et al[59] also determined that the air quality in confined spaces was affected by both TCs and ECs. More research is warranted concerning the long-term active use of and passive exposure to EC. The research performed by Song et al[60] determined that the use of ECs containing the carriers PG and vegetable glycerin produces inflammatory changes in the lungs that is dose responsive. Further research is needed to understand the significance of the magnitude of the dose responsiveness of PG and vegetable glycerin as well as flavors.

According to Biondi-Zoccai et al,[61] the use of TCs, ECs, or HNBC was associated with acute detrimental effects on oxidative stress, antioxidant reserve, platelet function, and hemodynamic parameters. The HNBC was associated with less biological and physiological markers of damage but requires further studies, along with ECs and TCs, to compare the long-term effects of use to the cardiovascular system. The findings obtained from the study performed by Gonzalez and Cooke[62] showed increases in mean arterial pressure and heart rate with inhibition of muscle sympathetic nerve activity when participants inhaled ECs with nicotine containing EC liquid. Gonzalez and Cooke[62] also found that inhalation of an EC with non-nicotine containing EC liquid did not elicit sympathoexcitatory responses or influence peripheral sympathetic outflow. However, because this study was performed on healthy, young individuals, the populations whose baroreflex function is not as robust is thought to likely experience exaggerated symptoms of sympathoexcitation, which warrants further research investigating the potential chronic effects of EC use on cardiovascular health. Chaumont et al[63] determined that short-term cessation of EC use in those who regularly use ECs decreases hemodynamic parameters, increases ventilatory function, and modified urine cigarettes signature[64]. Regardless of the nicotine content of EC liquid, transcutaneous oxygen tension levels decreased with EC use. Further research is necessary to determine if chronic cessation can further improve hemodynamic and pulmonary parameters.

Discussion

The neurological effects associated with the use of ECs include the alteration in the concentration of excitatory and inhibitory neurotransmitters in the mesocorticolimbic brain regions. These neurotransmitters are important factors in maintaining consciousness and normal brain function but also in the induction of and emergence from general anesthesia.[65] By

enhancing inhibiting excitatory transmission or inhibiting excitatory transmission, anesthesia providers can achieve desired anesthetic effects of sedation, amnesia, loss of consciousness, or muscle relaxation.[65, 66, 67] The anesthetic implications behind the changes to neurotransmitter concentrations associated with EC use can increase the risk for post-operative nausea and vomiting, increase neuronal excitability and requirements for sedatives, impact the effectiveness of commonly used medications in anesthesia, as well as delay emergence from anesthesia due to disturbances in neurotransmitter balance.[65, 66, 67] The damage to the neurovascular structures of the brain and potential contribution to cognitive dysfunction that ECs cause can significantly impact the emergence phase of anesthesia. Neurovascular damage can lead to impairment of cerebral autoregulation with decreased cerebral reserve, increased inflammation and oxidative stress, blood brain barrier disruption, and hemodynamic instability.[68, 69, 70] All of these factors can increase the risk for delayed emergence, alter the penetration of drugs into the brain further complicating emergence, and exacerbate or increase the risk for neurological injuries related to fluctuations in perfusion and oxygenation to the brain.[68, 69, 70]

The effects of ECs on the ocular health of individuals requiring anesthesia are important considerations to avoid potential perioperative complications. Important anesthetic considerations for patients with unstable tear film and moderate to severe dry eye is the increased risk for corneal damage related to the diminished blink reflex and exacerbation of dryness which could lead to a number of keratopathies.[71, 72] Additionally, some commonly used anesthetic medications such as anticholinergics and opioids can worsen ocular symptoms through varying mechanisms and cause further damage.[71, 72] Though the presence of postoperative ocular complications are rare following general anesthesia, in the presence of dry eyes or unstable tear film, the recommendation is to utilize appropriate ocular occlusion with a lubricating ointment

prior to placing eye protection.[73] The overproduction of tears may provide challenges during the intraoperative period in distinguishing between natural tear production and the presence of injury.[74, 75] The overproduction of tears may prove troublesome in maintaining proper eye protection during extended surgical procedures as well as recognize the entry into phase two of anesthesia during the emergence process.[74, 75] Finally, with increasing corneal thickness the anatomy of the eye and the structures that surround and support it may change which could increase the risk for injury or affect the distribution of local anesthetic administered during a retrobulbar or peribulbar block.[75, 76, 77] With increasing corneal thickness, changes to intraocular pressure could also occur, which may lead to negative postoperative outcomes given the techniques employed during induction, extreme surgical positioning, medications administered throughout the perioperative period, and if any major hemodynamic changes occur.[75, 76, 77, 78]

The anesthetic implications for alterations in the oral mucosa cells of EC users involves impaired oral mucosa integrity resulting in impaired healing and increased infection risk, the need for gentle airway management due to an enhanced inflammatory response, and regional anesthetic considerations for dental and oral surgery.[79, 80, 81, 82] The need for gentle airway management may require the pretreatment of oral mucosa with topical medications and the use of video laryngoscopy techniques in order to avoid unanticipated trauma to the oral cavity and airway.[79, 80, 81] The changes noted in the oral cavity and the airway may also increase difficulty with intubation and may necessitate advanced techniques to avoid unintentional damage.[81] Administration of anti-inflammatory agents like corticosteroids may be warranted to decrease the risk for post-extubation swelling.[80, 81] Additionally, when the oral mucosa is compromised the use of regional anesthesia may be inappropriate, resulting in the requirement for adjustment in anesthetic technique or plan of care.[82]

The anesthetic management of a patient who uses ECs can be complex.[3] With derangements in pulmonary function due to acute or chronic use of ECs, the patient can be at risk for increased respiratory complications and challenges when it comes to ventilation.[3, 64, 83, 84] Intraoperative management and emergence from anesthesia may be complicated and should involve optimizing the patient to prevent negative outcomes. Intraoperative management should include continuous monitoring of oxygen saturation and end tidal carbon dioxide concentration supplemented with arterial blood gas analysis to ensure optimization of oxygenation is occurring and ventilation/perfusion mismatch is being avoided.[83] Prolonged emergence and delayed return of airway reflexes can occur due to slower clearance of anesthetic gases so all objective criteria for extubation should be met prior to removal of protective airway devices.[83, 84] Inflammatory processes occurring in the lungs and airway increase the risk for bronchospasms, atelectasis, and laryngospasm.[83, 84] Administration of anesthetic gases and intravenous medications should be chosen carefully to avoid increased reactivity of the airway.[84] The anesthesia provider may consider treating with bronchodilators, anticholinergics, or corticosteroids during the preoperative phase to optimize the patient prior to the induction of anesthesia.[83, 84] Consideration of regional anesthesia is also warranted to minimize pulmonary complications.[64] Given the air quality studies performed, these anesthetic considerations may be indicated for patients who experience passive exposure to ECs however, more research is required to determine the long-term effects.[84]

The cardiovascular changes observed in patients who vape place the individual at risk for intraoperative complications that are similar to those risks associated with TC smoking. Due to the alterations in baseline hemodynamics, patients may be at greater risk of cardiac complications such as intraoperative myocardial infarction, cardiac arrhythmias, and

hemodynamic instability partially due to impaired baroreceptor response.[85, 86] Advanced hemodynamic monitoring may be necessary in order to closely monitor cardiovascular status and prevent negative perioperative outcomes.[85, 87] Along with close monitoring, careful fluid management should take place to maintain appropriate fluid balance and large swings in hemodynamic parameters.[86] An important consideration during the intraoperative phase for patients who vape ECs containing nicotine is the potential for nicotine withdrawal which manifests as increased levels of anxiety in the preoperative period and increased heart rate and blood pressure during the intraoperative period.[3, 85, 86] Management of nicotine withdrawal for longer duration surgical procedures may require increased anxiolytics or nicotine replacement therapy.[3, 85, 86] Similar to smoking TCs, individuals who vape ECs have increased risk of vasospasms due to endothelial dysfunction, which is caused by increased oxidative stress and decreased antioxidant status, further exacerbated by the use of ECs.[88] Maintenance of stable hemodynamics and fluid status is the recommendation to avoid worsening of endothelial dysfunction.[88] Consider avoiding use of nitrous oxide, as its use has been associated with decreased postoperative endothelial function and may worsen status.[88] Increased platelet activation raises the intraoperative risk for thrombosis so careful monitoring is recommended or even consultation with a hematologist if laboratory values are extremely deranged.[89]

Very few current preoperative assessment tools exist for patients who use ECs. One that was found within the literature by a large urban teaching hospital located in South Florida has shown clinically significant improvements in the identification of patients who use ECs and their likelihood of adverse perioperative outcomes.[50] The quantification of use (never, former, or current), type of EC liquid consumed which is additive specific, use per day, and number of years of vaping history are included in this pilot project with the addition of any treatment for

cessation of vaping, a readiness for change assessment, as well as an indicator for positive passive exposure.[50] When determining risk cardiopulmonary risk assessment with traditional cigarettes the quantification of use, use per day, and number of years of smoking history is established.[51] An important question that is asked of current traditional cigarette smokers is if they have abstained from smoking prior to their procedure and if so, for what duration of time as there are known benefits to abstinence from smoking prior to surgery.[52] This guides the anesthesia provider in determining which methods will be best suited for this particular patient in order to deliver safe and effective anesthesia during the perioperative period.[52] Given the duration in which the patient has abstained from smoking, if they have at all, will provide valuable insight as to the type of anesthetic to deliver (regional versus general versus monitored anesthesia care), the type of inhalational agents to use or not use, intravenous medications that can be utilized to prevent unwanted side effects associated with nicotine or tobacco products, and the anticipation of potential intraoperative events.[52] A similar assessment can be utilized for patients who use ECs however, the quantification of nicotine or "cartridges per day" must be calculated to accurately understand risk, anticipate complications, and provide safe anesthesia.[52] The importance lies in how to properly assess and evaluate patients who use ECs and if further pulmonary or cardiac testing is indicated based on use to eliminate or anticipate perioperative complications when delivering anesthesia.[52]

Conclusion

The increasing number of potential surgical patients who use ECs requires the knowledge and evolution of anesthetic care during surgical procedures to help optimize perioperative outcomes and prevent unanticipated negative complications. The anesthesia providers who partake in an educational intervention regarding the health hazards associated with the acute and

chronic use of ECs can make a difference in the care provided by improving their knowledge and skills in the perioperative period. The studies provided have their limitations, mainly being small sample sizes and the need for more research in a real life setting rather than a controlled environment. However, the potential for advancing anesthesia practice with continued education practice will allow for increased patient safety and overall patient outcomes.

Purpose/PICO Clinical Questions/Objectives

PICO Question or Purpose

The purpose of this project was to educate anesthesia providers on the negative side effects associated with the acute and chronic use of ECs and in what manner the use of ECs affects the anesthetics administered during surgery or diagnostic procedures. This project was also for discussion regarding the proper perioperative management of patients who have history of current or past use of ECs. Additionally, this project informed anesthesia providers on the importance of proper preoperative assessment for the patient populations that use ECs or are exposed to ECs via surrogate or secondhand vaping. This was done via the utilization of a preoperative assessment tool that was meant to help to determine intraoperative cardiopulmonary risk.

The PICO question for this project was as follows: Will an educational intervention regarding the anesthetic perioperative consequences of EC use improve the knowledge among anesthesia providers?

P: Any aged individual who acutely or chronically uses ECs as well as those patient populations who are exposed to secondhand vapor from ECs.

I: An educational intervention, developed from evidence-based literature, with the goals of improving the anesthesia provider's knowledge of the health hazards of ECs and the impact ECs may have in the perioperative period to guide intraoperative management

C: The anesthesia provider's pre-education knowledge measured by a pretest containing questions from the literature relating to the potential anesthetic consequences of EC use.

O: The anesthesia provider's post-education knowledge that will be evaluated by a posttest containing questions from evidence-based literature pertaining to the anesthetic consequences of EC use in the perioperative period.

Primary DNP Project Goal

The health hazards surrounding the use of or exposure to vapor from electronic cigarettes in the perioperative period can lead to unanticipated intraoperative challenges like difficulty with intubation, pulmonary injury, and hemodynamic instability.[3, 5] These intraoperative challenges can increase anesthesia related complications such as dangerous drops in oxygen saturations due to difficult intubation, unexpected ICU admission due to pulmonary injury, and increased risk for intraoperative cardiac events due to unstable hemodynamics.[3,5] The use of electronic cigarettes is a fairly current and new trend amongst multiple population groups that, until recently, has lacked substantial evidence based data involving the health hazards associated with their use. This remains especially complex for patients undergoing procedures that require anesthesia because there is no standardized preoperative evaluation to quantify perioperative risk and guide intraoperative management. The purpose of this project was to educate anesthesia providers on the potential negative side effects associated with the acute and chronic use of electronic cigarettes and to help guide anesthetic administration and management during surgery or diagnostic procedures.

The practice site was a large urban teaching facility located in South Florida. Their mission was to "heal the body, mind, and spirit of those we touch."[90] Their leadership team was made up a board of commissioners that consisted of 7 members appointed by the governor of Florida. This site was one of the largest not for profit facilities and was important for this project because of the large number of high acuity patients in the community.[90] This facility houses 571 beds and has over 14,000 employees, and as of 2022, this facility had a total number of 10,567 surgeries including but not limited to: bariatric, hernia repair, general, emergency, neurologic, cardiac, orthopedic, vascular, transplant, and advanced minimally invasive surgeries.[90] The high number of procedures performed at this facility, increases the likelihood that patients who vape will be admitted to or arrive via outpatient channels for surgery.

According the National Center for Health Statistics and the Centers for Disease Control and Prevention (CDC), in the US, approximately 8.1 million adults and 2.55 million adolescents use electronic cigarettes with frequency of use most commonly being daily or weekly.[91, 92] Additionally, electronic cigarettes remain unregulated by the US Food and Drug Administration (FDA) allowing for widespread sale and accessibility for individuals over the age of 18 years, in most states, as of 2021.[92] Users of electronic cigarettes identify as a separate group from those who "smoke cigarettes" and prefer to describe themselves as individuals who "vape."[91] The vernacular used to describe the use of electronic cigarettes has evolved from utilization of the word "smoking" and users of electronic cigarettes consider themselves not to be "smokers," which can complicate a health care provider's assessment of smoking status in the primary care environment as well as in the perioperative period.[4] When discussing these statistics with providers at this facility, it was determined that there was not a section within the preoperative assessment documentation for vaping status.

The practice at this facility was that the anesthesia provider performs a preoperative evaluation, but the documentation was performed by the attending anesthesiologist. There was no section within the preoperative assessment documentation to determine vaping status. The literature supports including a subsection to determine vaping status in order to better provide intraoperative management.[51] Intraoperative management varies per anesthesia provider based on the training and experience they have as well as the presence or absence of other patient comorbidities. Due to these factors, it was not possible to discuss how intraoperative management of patients who vape was performed at this site. It was noted that these patients usually are treated as if they are current traditional cigarette smokers.

The project sponsor for this project played a major role in determining whether the educational points were of interest and importance to the anesthesia providers at this facility. This individual served as a mentor and helped to navigate certain issues and problems regarding the nature of the project design and how one should best deliver information. Additionally, the project sponsor helped to identify major leaders within the facility who helped to motivate and encourage other providers to participate in this project. The sample included approximately 60 total anesthesia providers consisting of anesthesiologists, anesthesiologist assistants, and certified registered nurse anesthetists working in the surgical department of this facility. This population was important to this project due to the direct relation to the information which was provided to the patient population that this group provides anesthesia services for. The update in evidence-based literature allowed these anesthesia providers to best care for their patients who vape, bettering patient outcomes. This facility met and exceeded the goals set forth in order to have increased quality of patient experience, effective quality of care, and patient safety.[90] This

facility's dedication to these goals provided one with the ability to reach a large target audience to further improve patient satisfaction, overall quality of care, and patient safety.[90]

Goals and Outcomes

For the purposes of this DNP quality improvement project, the following SMART objectives were identified:

Specific

Anesthesia providers received an educational intervention tool with evidence-based information on the organ specific side effects of electronic cigarettes in order to improve anesthetic management during the perioperative period

Measurable

The effectiveness of this educational intervention was derived through the analysis of a survey that was provided to participants before and after delivery of the educational presentation. Outcomes were measured by evaluating the variations in the anesthesia providers' knowledge of the negative side effects associated with electronic cigarettes and perioperative management techniques for this patient population, pre- and post-intervention. In order to generate reports, Qualtrics® software was used to create the surveys and analyze the data.

Achievable

Physician anesthesiologists, certified registered nurse anesthetists (CRNAs), and certified anesthesiologist assistants (CAAs) and other anesthesia providers benefited from the educational intervention of negative side effects associated with electronic cigarettes and perioperative management techniques for the patient who vapes.

Realistic

Anesthesia providers were educated on the negative side effects associated with the use of electronic cigarettes for surgical patients and potential perioperative management techniques that can be utilized to avoid complications.

Timely

The presentation discussing the negative side effects associated with the use of electronic cigarettes and the potential perioperative management techniques that can be implemented to decrease the risk for complications was completed and available to anesthesia providers within 6 months. The outcome of this initiative was as follows: within 6 months, anesthesia providers had access to an evidence-based presentation discussing the organ specific side effects associated with the use of electronic cigarettes and the recommendations for perioperative management for the vaping patient who requires surgical intervention.

Program Structure

Following guidance from the DNP student's clinical mentor, a baseline organizational needs assessment was performed at the potential project site. This needs assessment was performed mainly through interviewing various anesthesia providers followed by a review of the preoperative assessment documentation paperwork. A thorough review yielded a section in the preoperative assessment documentation titled "Social Activities" where alcohol consumption and quantification of nicotine containing tobacco products was located. Discussion amongst several anesthesia providers led to an overwhelming agreement that this section would be an appropriate location for information pertaining to electronic cigarette use and updated vaping status. A secondary interview style assessment was performed by the clinical mentor to gauge interest in the topic of anesthesia implications for the vaping patient with several providers showing

interest. The DNP student was successful in the completion of this project due to the approval and encouragement with the chief certified registered nurse anesthetist along with the chief anesthesiologist.

Strengths

The strengths that were identified at this facility that aided in the completion of this project were the specialized services that are offered, the updated technology and facilities available for use, the skilled staff that were essential providing excellent care, and this facility's reputation for excellence.[90] The ability of a large hospital to provide specialized services allows for a wide variety of patients from different cultures and demographic backgrounds to seek treatment at this facility.[93] With increasing patient needs and attendance, there was an increased likelihood that patients who use electronic cigarettes required specialized surgical services.[90] The fact that this facility was equipped with state-of-the-art medical equipment means that they value new information to better patient care.[90] This increased the likelihood that this project was accepted at this facility. Having skilled staff and an excellent reputation continues to support this idea that new evidence-based information and knowledge provided for better patient care and outcomes.[90]

Weaknesses

The weaknesses that were identified at this facility that might hinder the completion of this project are capacity constraints, dependence on external funding, and competition.[90] Any facility experiences capacity constraints, no matter how large the hospital or the number of beds they have.[90] With capacity nearing complete, this might translate into patient care delays or increased pressure on existing resources which could have placed this project at a lower priority.[90] Additionally, this facility was dependent on government funding to provide services

that may have affected operations should changes in policies or disasters occur.[90] Finally, the local competition among hospitals may have affected the choice a patient makes when choosing which hospital to attend.[93] These factors might have slowed the progression of this project.

Opportunities

The opportunities that were identified at this facility that may have increased the chances for this project to be completed are population growth, medical tourism, and healthcare legislation.[90] With an ever-growing population in South Florida, there was a need for this facility to potentially require expansion due to increased patient influx.[90] This facility has many specialized surgical services that increase the number of patients seen at this site.[90] Additionally, evolving healthcare legislation allows the hospital to adapt and optimize the way surgical services are run, therefore increasing efficiency.[93] These site-specific opportunities increased the likelihood that the anesthesia providers who maintain leadership positions saw the importance in this project and supported it.

Threats

The threats that were identified at this facility that might have ceased the advancement of this project are regulatory changes and the current anesthesia provider shortage. Regulatory changes are something that remain out of the control of those individuals who supported this project.[93] Should regulatory changes have occurred within the facility, this project may have become low on the priority list due to the impact these changes may have had on the financial stability and overall hospital operations.[93] Additionally, the anesthesia provider shortage might not have allowed for this project to be seen as important. With the shortage of providers, the quality of patient care can decrease, making the priority of the surgical department those things that they can do quickly to increase safety and quality of care.[93]

Methodology of Quality Improvement

Setting and Participants

A baseline organizational needs assessment was performed at the project site. This needs assessment was performed mainly through interviewing various anesthesia providers followed by a review of the preoperative assessment documentation paperwork. A thorough review yielded a section in the preoperative assessment documentation titled “social activities” where alcohol consumption and quantification of nicotine containing tobacco products was located. Discussion amongst several anesthesia providers led to an overwhelming agreement that this section would be an appropriate location for information pertaining to electronic cigarette use and updated vaping status. A secondary interview style assessment was performed by the clinical mentor to gauge interest in the topic of anesthesia implications for the vaping patient with several providers showing interest. The successful completion of this project required the chief certified registered nurse anesthetist along with the chief anesthesiologist’s approval and encouragement to garner additional interest among anesthesia providers at this facility. The relevance of the sample size and setting in which this project took place was important due to evolving nature of the health hazards associated with the use of ECs.

Description of Approach and Project Procedures

This DNP project began with inviting all of the anesthesia providers at this facility to participate in the quality improvement project. The method employed for this project was that of a pre-post intervention design that would first measure self-reported knowledge on the health hazards of ECs with respect to anesthesia administration. The data collected before the educational intervention included demographic data, position or title, years of practice, and educational level. The educational intervention included the system-based health hazards

associated with the acute and chronic use of ECs, the anesthetic implications of these health hazards, and the evaluation of a preoperative assessment tool in determining risk for anesthesia complications during the perioperative period. Throughout the educational intervention, providers were invited to speak openly about their own experiences with patients who vape and undergo anesthesia. In order to maximize the educational intervention, the DNP student welcomed discussion amongst individuals regarding adverse events and treatment options pursued to discourage negative perioperative outcomes. The project investigator attempted to create an educational intervention that had a duration of approximately 20 minutes. Following the educational intervention, participants were asked to complete a post-test survey.

Protection of Human Subjects

The plan for protection of human subjects was to utilize the Florida International University Institutional Review Board and any other Institutional Review Board that the facility requires. Participants were asked to consent via Qualtrics, with the right to withdraw at any time. Benefits of participation included the improvement of knowledge in preventing negative patient outcomes, intraoperative management, and self-reflection on anesthetic methods and practice. No identifiable data was collected during this project. Data was collected and stored in a password-protected online database, accessible only to the primary investigator.

Data Collection

The data collection included demographic information including gender, race, and ethnicity. The participant's position or title was included in the collection of data along with the highest educational level achieved. Additionally, the years of practice were included in the data collection. This information, along with the pre-test and post-test, were obtained via a Qualtrics survey.

Data Management and Analysis

Data storage and analysis were done via a password-protected and locked account in Qualtrics. Data were collected and stored this way in an electronic database. The primary investigator was the only individual with access. No direct identifiers were collected, and all results were reported in collectively. Questionnaires were collected, scored, and presented as percentages for comparison of pre- and post-educational intervention.

Results

Demographics

The demographics of the participants surveyed are represented below.

Table 1. Consent to Participate

Answer	Percentage	Count
I consent to be a participant	100.00%	10
Total	100.00%	10

Table 2. Gender

Answer	Percentage	Count
Male	40.00%	4
Female	60.00%	6
Non-binary or third gender	0.00%	0
Other	0.00%	0

Table 3. Age in Years

Answer	Percentage	Count
25-30	20.00%	2
31-35	50.00%	5

36-40	10.00%	1
41+	20.00%	2

Table 4. Ethnicity

Answer	Percentage	Count
Hispanic	50.00%	5
Caucasian	40.00%	4
African American/Black	10.00%	1
Asian	0.00%	0
Other	0.00%	0

Table 5. Position/Title

Answer	Percentage	Count
CRNA	80.00%	8
MD	20.00%	2
AA	0.00%	0

Table 6. Level of Education

Answer	Percentage	Count
Certificate	0.00%	0
Bachelors	0.00%	0
Masters	20.00%	2
Doctorate (MD/DO/PhD/DNP)	80.00%	8

Table 7. Experience in Anesthesia in Years

Answer	Percentage	Count
1-2	40.00%	4

2-5	40.00%	4
5-10	10.00%	1
10+	10.00%	1

A total of 66 invitations were distributed via email to anesthesia providers to participate in the pre- and post-test educational intervention. Ten participants consented to participate, no surveys were left incomplete, totaling 10 participants for the quality improvement project. The demographics of those who participated are represented by the following: male (*n* = 4, 40%), female (*n* = 6, 60%), Hispanic (*n* = 5, 50%), Caucasian (*n* = 4, 40%), and African American (*n* = 1, 10%). Eight of the participants were certified registered nurse anesthetists (*n* = 8), with either a master's degree (*n* = 2, 20%) or a doctorate (*n* = 6, 60%), and 1-2 years of experience (*n* = 3, 30%), 2-5 years of experience (*n* = 4, 40%), or 5-10 years (*n* = 1, 10%) as an anesthesia provider. Two participants were medical doctors (*n* = 2, 20%) with 1-2 years of experience (*n* = 1, 10%) or 10 or more years of experience (*n* = 1, 10%) as an anesthesia provider.

Pre-Test Knowledge of Anesthesia Implications for Patients Who Vape

The pre-test consisted of 10 questions that assessed the current knowledge of the anesthesia implications for patients who vape. None of the participants were able to identify that an increased plaque buildup is a complication noted in patients who vape. The same number of participants were unable to identify that strawberry is a vape flavor that increases the risk for airway hyperresponsiveness when compared to other flavors. One (*n* = 1, 10%) out of 10 participants was able to determine that one of the neurotransmitters effected by ECs was GABA. The same number of participants correctly identified that an increase in tear production occurs and that an increased requirement for anxiolytics is noted in those patients who vape. Two (*n* = 2, 20%) of the ten participants correctly answered that the estimated number of adults and

adolescents in the United States that use ECs is 10 million. Four (*n* = 4, 40%) of the 10 participants answered that increased airway reactivity was a pulmonary complication associated with the use of ECs, and 5 (n = 5, 50%) of the 10 participants correctly identified that an increased risk of vasospasms occurs in patients who vape. Seven (*n* = 7, 70%) of the 10 participants were able to identify that delayed wound healing, sepsis, and EVALI were all poor patient outcomes that could occur when patients undergo anesthesia without an anesthesia provider's knowledge of their vaping history. No questions were marked invalid.

Post-Test Knowledge of Anesthesia Implications for Patients Who Vape

After the educational intervention, participants answered a post-intervention questionnaire consisting of the same questions found in the pre-test. Results assessed the knowledge gained from the educational intervention are listed in the table below (Table 1). All questions showed an increase in the correct answer when the pre- and post-intervention tests were compared. The most significant increase in participant knowledge was noted in the application questions discussing which EC flavor the participant would be most concerned with in the preoperative area with regard to increased airway hyperresponsiveness, where in the pre-test none of the participants answered correctly and, in the post-test, all 10 of the participants answered correctly, demonstrating an increase in participant knowledge by 100.0%. Of note, participant knowledge was shown to increase by 90.0% when comparing the pre-test and the post-test answers with respect to the neurotransmitter most likely to be affected by the use of ECs. In addition to the 2 questions discussed above, 5 further questions demonstrated 50.0% or higher increase in participant knowledge when comparing the pre- and post-test. Of the 10 questions provided, only 3 provided less than a 50.0% increase in participant knowledge with none of the questions dropping below less than a 30.0% increase in participant knowledge.

Table 8. Pre-Test and Post-Test Responses

Question	Pre-Test (n = 10)	Post-Test (n = 10)	Difference (%)
What is the estimated number of adults and adolescents in the United States who use Electronic Cigarettes?	2	8	+60.00
Which of the following complications or poor patient outcomes can occur when patients undergo anesthesia without the anesthesia provider knowing their vaping history?	7	10	+30.0
Which of the following neurotransmitter derangements is correct for the patient who vapes?	1	10	+90.0
Which of the following are anesthetic implications for the neurological system for the patient who vapes?	0	7	+70.0
Which of the following are anesthetic implications for the ocular system for the patient who vapes?	1	5	+40.0
Which of the following are anesthetic implications for the oropharyngeal system for the patient who vapes?	0	7	+70.0
Which of the following are anesthetic implications for the pulmonary system for the patient who vapes?	4	9	+50.0
Which of the following are anesthetic implications for the cardiovascular system for the patient who vapes?	5	8	+30.0
Which of the following are anesthetic implications for the nicotine withdrawal for the patient who vapes?	1	6	+50.0
Your patient in the preoperative area admits they vape. Which of the following Electronic Cigarette flavors	0	10	+100.0

are you most worried about due to increased airway hyperresponsiveness?

Summary of Data

Overall, the results of the educational intervention demonstrated a knowledge increase of 59.0% between the pre- and post-tests. The most significant increase in provider knowledge was noted in the questions that discussed which flavor would be most concerning for increased airway hyperresponsiveness (+100.0%) and the neurotransmitter derangement that would be most likely to occur in patients who vape (+90.0%). The following figures illustrate the differences between the pre- and post-test answers for each question.

Figure 1. Question 1 Responses

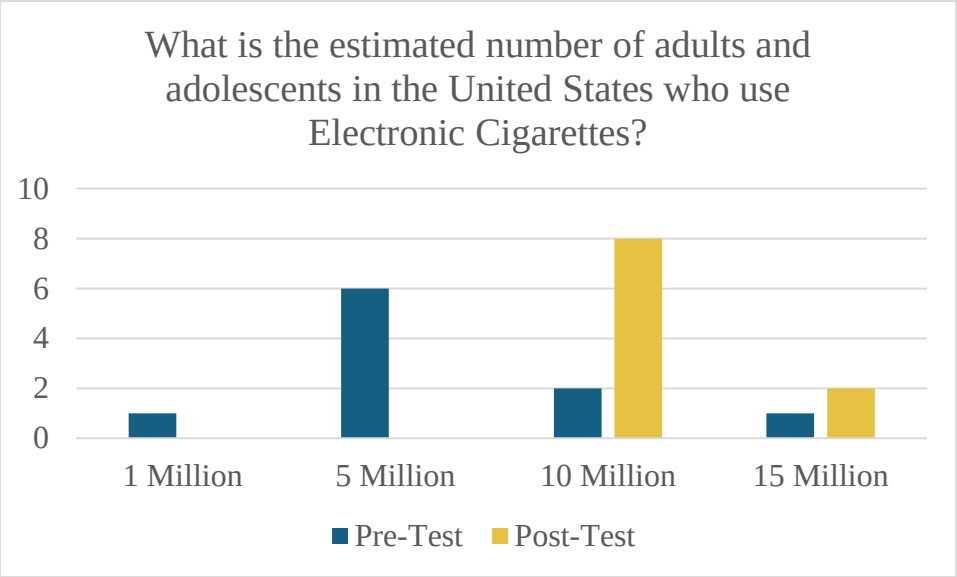


Figure 2. Question 2 Responses

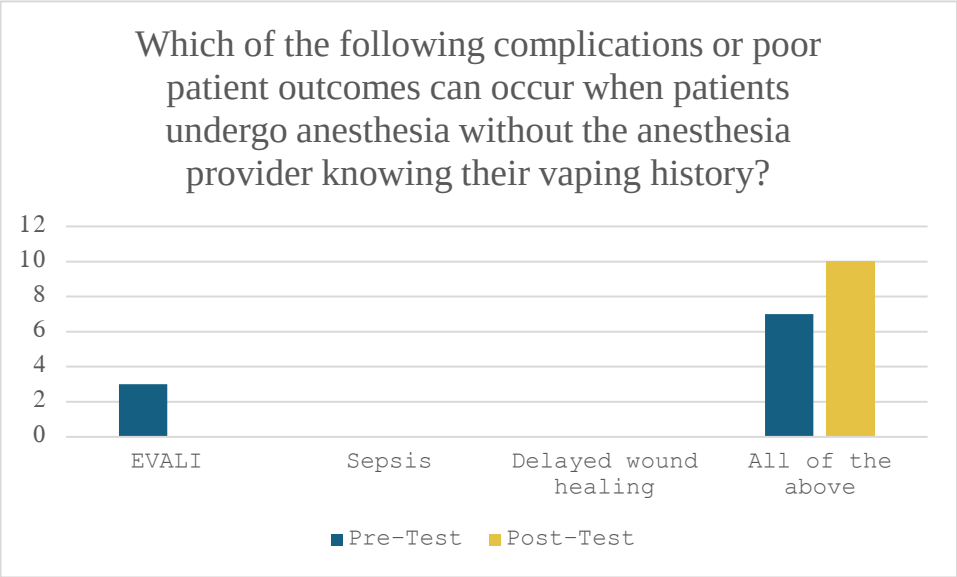


Figure 3. Question 3 Responses

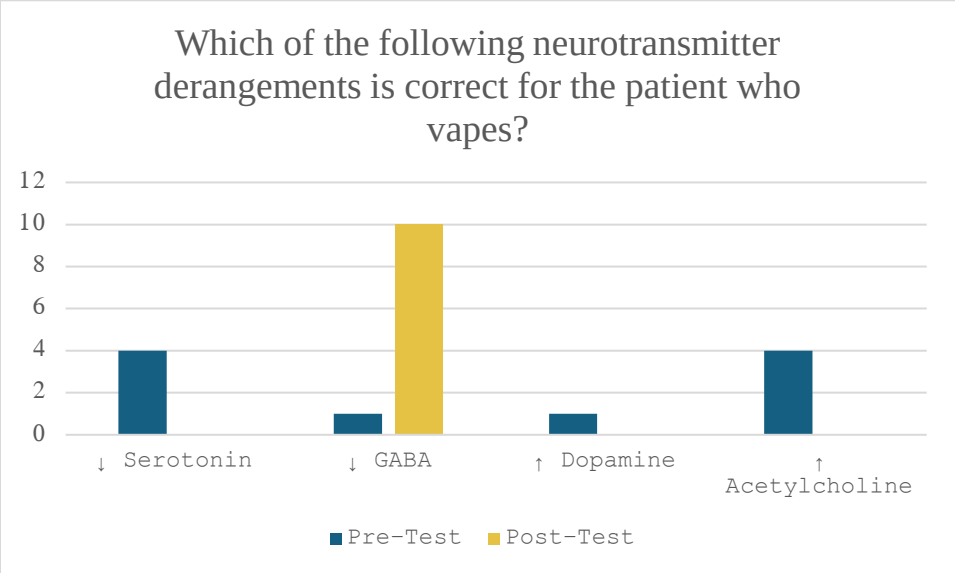


Figure 4. Question 4 Responses

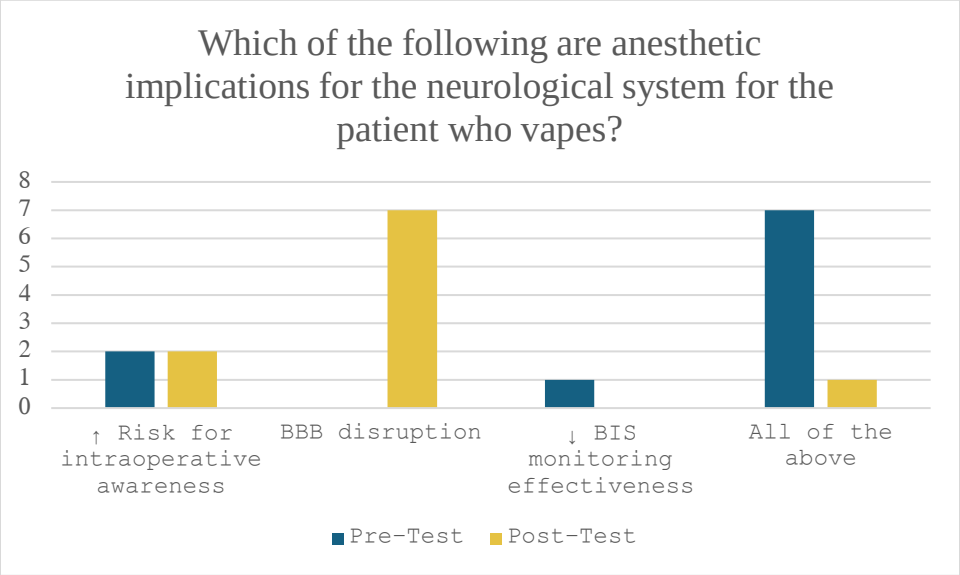


Figure 5. Question 5 Responses

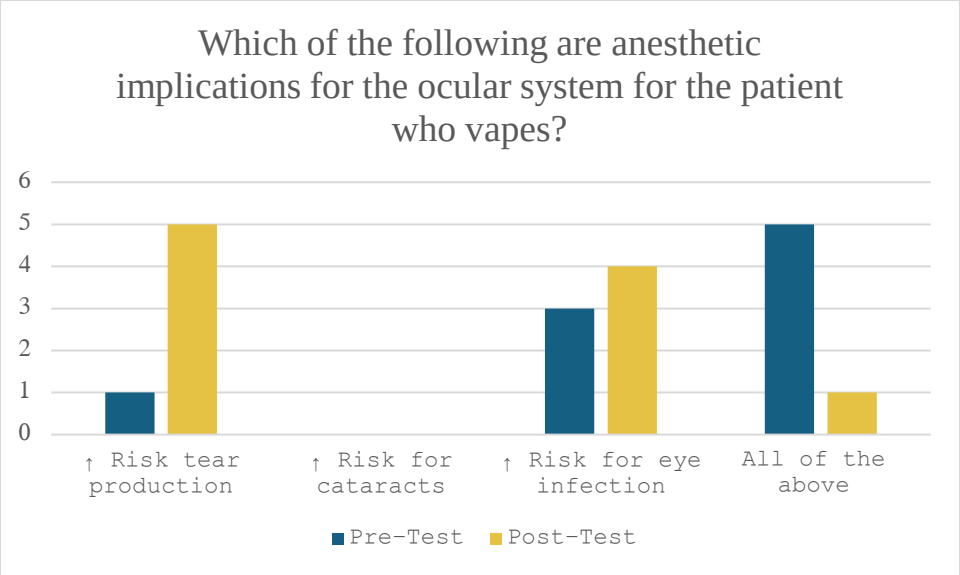


Figure 6. Question 6 Responses

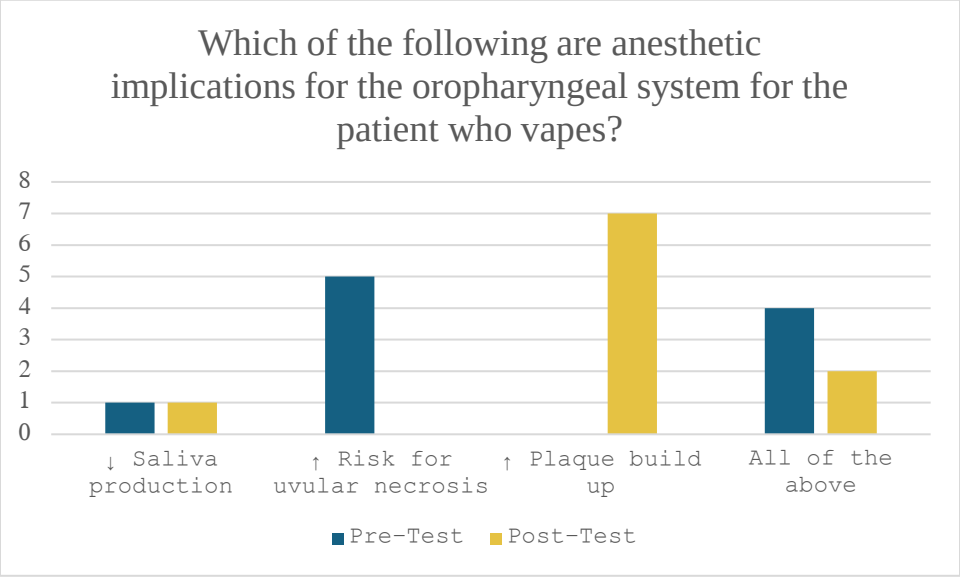


Figure 7. Question 7 Responses

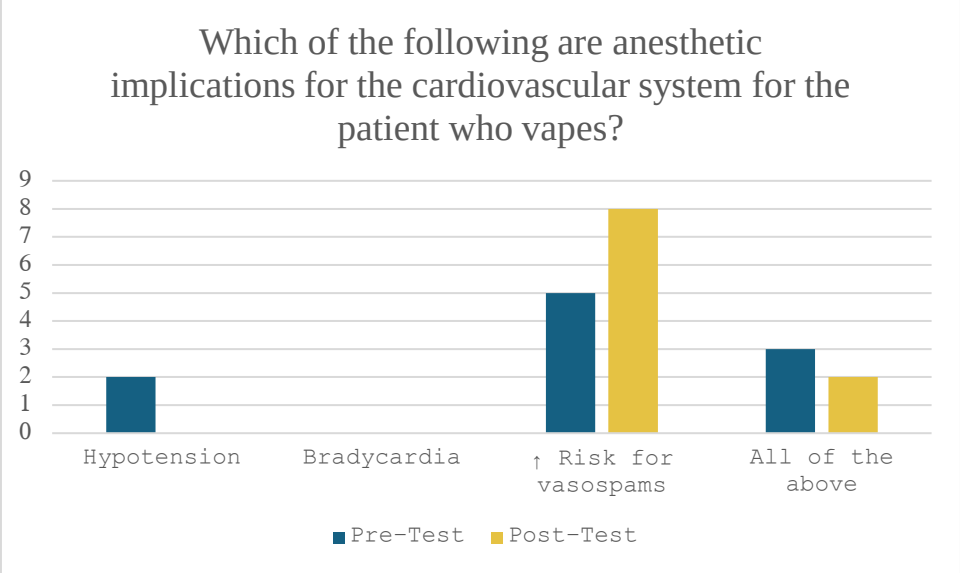


Figure 8. Question 8 Responses

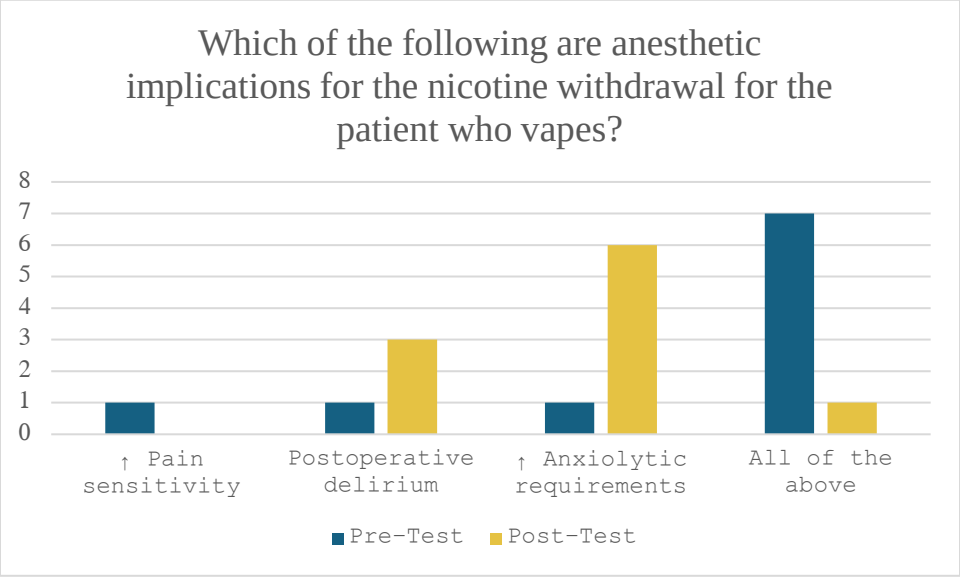


Figure 9. Question 9 Responses

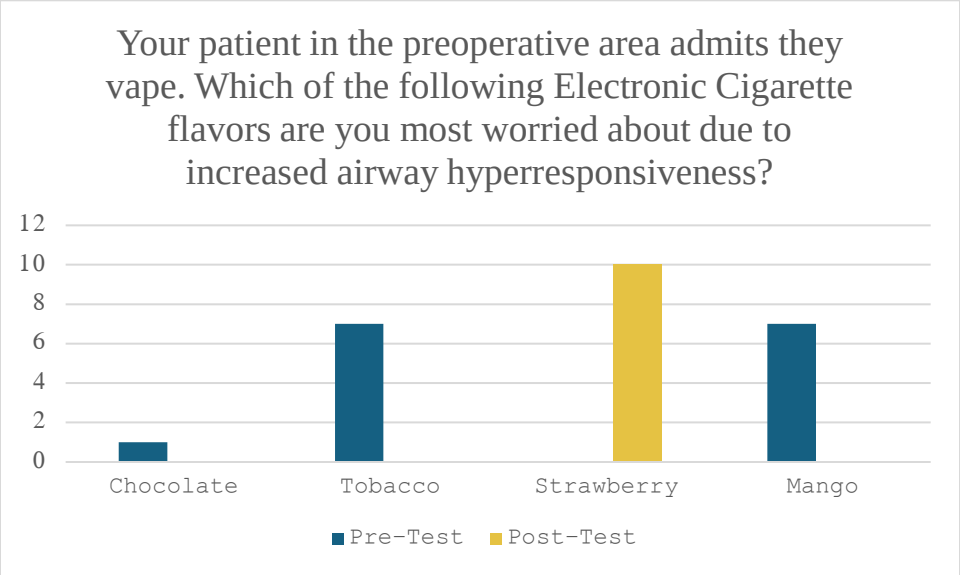
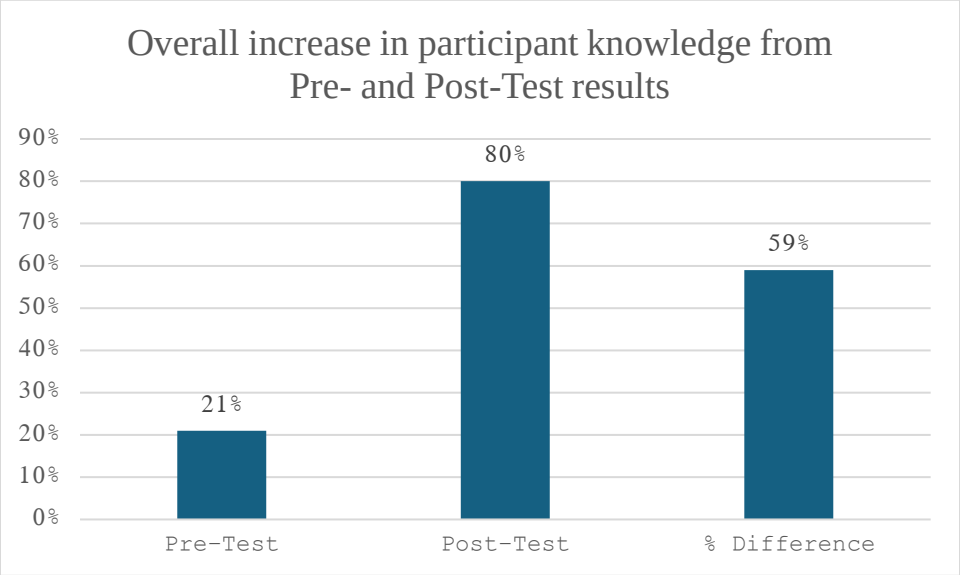


Figure 10. Question 10 Responses



Limitations

This quality improvement project had several limitations including a small sample size. A total of 66 surveys were distributed via email to anesthesia providers at one location, however, only 10 participants completed the pre-test, educational intervention, and post-test in its entirety. A larger, more diverse sample size would allow for a more accurate representation of the preexisting knowledge of the anesthetic implications for patients who vape.[94] A larger sample size would also validate the effectiveness of the educational module and intervention.[94] The time frame for the responses was also a limitation, as participants were given 2 months to complete the survey. Another limitation was sending out the surveys to only 1 facility instead of multiple facilities to maximize the amount of participation. The need for further research was an additional limitation for this project. One area of future research is in the pathway that nicotine is metabolized by and how it affects the many anesthetic agents that are metabolized by the same pathways or ones that share end target organs. Another area of future research is in the

components of the EC liquid and how they impact various organ systems on the cellular and molecular level, independent of nicotine.

Discussion of the Results with Implications for Advanced Nursing Practice

The preoperative evaluation phase of the perioperative period is a vital part of the anesthetic management plan set forth by the anesthesia provider. Understanding how to properly communicate with the patient regarding their vaping status in the preoperative phase is essential in determining how to manage potential complications that can be expected during the intraoperative and postoperative phase. By gathering a thorough and exhaustive history of a patient's vaping use, the anesthesia provider can tailor the patient's unique anesthetic to avoid the complications that this project discusses. The results of this project indicate that there is a knowledge gap and that anesthesia providers can improve patient outcomes by understanding how the use of ECs impacts major organ systems in the body.

This project will prepare the anesthesia provider to be aware of the potential perioperative changes that are significant to this patient population. The increased requirement for anxiolytics and a meticulous airway assessment is vital during the preoperative phase to properly optimize patients who vape.[65, 66, 67, 83, 84] Additionally, the probable need for a preoperative breathing treatment due to airway hyperresponsiveness related to EC liquid flavors and the potential utilization of regional anesthetic techniques due to a reactive airway process are important factors to consider in this patient population.[83, 84] A unique consideration for outpatient eye centers or those patients presenting for ocular surgery is the anatomical changes that can occur to the eye in patients who vape, which may complicate regional anesthesia.[75, 76, 77] This project demonstrates that during the induction of anesthesia, the anesthesia provider should be aware of the increased requirements for sedatives and anesthetic agents.[66, 67] Important

considerations for the patient's eyes during the induction phase is that there is an increased risk for corneal abrasions, intraocular pressure changes, nystagmus, and overall ocular injury due to the vasoconstrictive effects of ECs.[71, 72] Additionally, gentle airway management should be considered not only due to increased plaque, tooth decay, and bleeding but also because of this patient's increased risk of infection and impaired healing abilities in the oropharynx.[79, 80, 81] This patient population may require video-laryngoscopy or pretreatment with topical medications.[79,80, 81] Lastly, the impaired baroreceptor response may cause dangerous hemodynamic swings during the induction phase.[85, 86] This project reveals that patients who vape are at an increased risk of post-operative nausea and vomiting, unlike their tobacco smoking counterparts.[65, 66, 67] An important aspect of the maintenance phase of anesthesia that this project discloses is the impairment of cerebral autoregulation, blood brain barrier disruption, and the decreased cerebral reserve that can impact the ability the length of stay in the hospital due to unwarranted postoperative effects.[68, 69, 70] The caution that is required during the maintenance phase due to the pulmonary changes demonstrated by this project suggest that vigilant ventilatory management should be observed due to decreased gas exchange, pulmonary function, and the mimicking of an obstructive process.[3, 64, 83, 84] Even passive exposure to ECs may cause these pulmonary changes during the intraoperative phase.[84] Additionally, this project displays that this patient population is at risk for hemodynamic instability and thrombosis, which places these individuals in danger due to the increased chances for intraoperative myocardial infarction or cardiac arrhythmias.[85, 86] Furthermore, the use of nitrous oxide should be avoided due to its association with worsening endothelial function, increasing the risk for thrombosis and coronary vasospasms.[88] This project shows that this patient population may experience delayed emergence and increased risk for emergence agitation, which may alter the anesthesia provider's choice in anesthetic

management.[65, 66, 67] This project demonstrates the potential need for the administration of corticosteroids during the emergence and post-operative phase to prevent any post-extubation swelling and postoperative complications during the recovery period.[80, 81]

This project can have positive implications for health care organizations that aim to offer the latest research and evidence-based practice approaches to the management and care of their patients who use products like ECs undergoing any surgical procedure. This project will help guide future research and standardization options for properly evaluating and managing patients who vape during the perioperative phase.

Conclusion

With the increasing number of individuals in the United States and the world using ECs, the anesthesia provider must maintain the responsibility of remaining up to date on all the potential complications that may arise during the perioperative phase of a patient's surgical experience. By performing a rigorous preoperative evaluation and assessment, proper planning and execution of an anesthetic that is tailored to the vaping patient's specific needs can ensure that patient outcomes are improved and overall surgical experiences are positive. The studies provided do have their limitations, mainly being small sample sizes and the need for further research. However, as anesthesia providers continue to improve their knowledge surrounding this growing vaping population, they also can improve their patient outcomes.

References

1. Le Foll B, Piper ME Fowler, CD et al. Tobacco and nicotine use. *Nat Rev Dis Primers.* 2022;8(19). https://doi.org/10.1038/s41572-022-00346-w
2. Ozgunay SE, Karasu D, Dulger S, Yilmaz C, Tabur Z. Relationship between cigarette smoking and the carbon monoxide concentration in the exhaled breath with perioperative respiratory complications. *Braz J Anesthesiol*. 2018;68(5):462-471. doi:10.1016/j.bjan.2018.02.006
3. Carrick MA, Robson JM, Thomas C. Smoking and anaesthesia. *BJA Educ*. 2019;19(1):1-6. doi:10.1016/j.bjae.2018.09.005
4. Electronic cigarettes. Centers for Disease Control and Prevention. July 12, 2021. Accessed August 29, 2023. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/index.htm.
5. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: umbrella and systematic review of the global evidence. *Med J Aust*. 2023;218(6):267-275. doi:10.5694/mja2.51890
6. Overbeek DL, Kass AP, Chiel LE, Boyer EW, Casey AM. A review of toxic effects of electronic cigarettes/vaping in adolescents and young adults. *Critical Reviews in Toxicology*. 2020;50(6):531-538. doi:10.1080/10408444.2020.1794443
7. Larue F, Tasbih T, Ribeiro PAB, Lavoie KL, Dolan E, Bacon SL. Immediate physiological effects of acute electronic cigarette use in humans: a systematic review and meta-analysis. *Respir Med*. 2021;190:106684. doi:10.1016/j.rmed.2021.106684
8. Ali N, Xavier J, Engur M, Pv M, Bernardino de la Serna J. The impact of e-cigarette exposure on different organ systems: a review of recent evidence and future perspectives. *J Hazard Mater*. 2023;457:131828. doi:10.1016/j.jhazmat.2023.131828
9. Jonas AM, Raj R. Vaping-related acute parenchymal lung injury: a systematic review. *Chest*. 2020;158(4):1555-1565. doi:10.1016/j.chest.2020.03.085
10. Tzortzi A, Kapetanstrataki M, Evangelopoulou V, Beghrakis P. A systematic literature review of e-cigarette-related illness and injury: not just for the respirologist. *Int J Environ Res Public Health*. 2020;17(7):2248. doi:10.3390/ijerph17072248
11. Meng XC, Guo XX, Peng ZY, Wang C, Liu R. Acute effects of electronic cigarettes on vascular endothelial function: a systematic review and meta-analysis of randomized controlled trials. *Eur J Prev Cardiol*. 2023;30(5):425-435. doi:10.1093/eurjpc/zwac248
12. Saz-Lara A, Martínez-Vizcaíno V, Sequí-Domínguez I, Álvarez-Bueno C, Notario-Pacheco B, Cavero-Redondo I. The effect of smoking and smoking cessation on arterial stiffness: a systematic review and meta-analysis. *Eur J Cardiovasc Nurs*. 2022;21(4):297-306. doi:10.1093/eurjcn/zvab102
13. Kennedy CD, van Schalkwyk MCI, McKee M, Pisinger C. The cardiovascular effects of electronic cigarettes: A systematic review of experimental studies. *Prev Med*. 2019;127:105770. doi:10.1016/j.ypmed.2019.105770
14. Garcia PD, Gornbein JA, Middlekauff HR. Cardiovascular autonomic effects of electronic cigarette use: a systematic review. *Clin Auton Res*. 2020;30(6):507-519. doi:10.1007/s10286-020-00683-4
15. Martinez-Morata I, Sanchez TR, Shimbo D, Navas-Acien A. Electronic cigarette use and blood pressure endpoints: a systematic review. *Curr Hypertens Rep*. 2020;23(1):2. doi:10.1007/s11906-020-01119-0

16. Rahman A, Alqaisi S, Alzakhari R, Saith S. Characterization and summarization of the impact of electronic cigarettes on the cardiovascular system: a systematic review and meta-analysis. *Cureus*. 2023;15(5):e39528. Published 2023 May 26. doi:10.7759/cureus.39528
17. Ruszkiewicz JA, Zhang Z, Gonçalves FM, Tizabi Y, Zelikoff JT, Aschner M. Neurotoxicity of e-cigarettes. *Food Chem Toxicol*. 2020;138:111245. doi:10.1016/j.fct.2020.111245
18. Stratford K, Kc P, Rudy S, Weidner AS, Callahan-Lyon P, Valerio LG Jr. Exploring the potential neurotoxicity of vaping vitamin E or vitamin E acetate. *Toxicol Appl Pharmacol*. 2022;434:115813. doi:10.1016/j.taap.2021.115813
19. Cascella M, Bimonte S, Muzio MR. Towards a better understanding of anesthesia emergence mechanisms: Research and clinical implications. *World J Methodol*. 2018;8(2):9-16. doi:10.5662/wjm.v8.i2.9
20. Martheswaran T, Shmunes MH, Ronquillo YC, Moshirfar M. The impact of vaping on ocular health: a literature review. *Int Ophthalmol*. 2021;41(8):2925-2932. doi:10.1007/s10792-021-01842-w
21. Md Isa NA, Koh PY, Doraj P. The tear function in electronic cigarette smokers. *Optom Vis Sci*. 2019;96(9):678-685. doi:10.1097/OPX.0000000000001422
22. Carmona MJC, Quintão VC. Comprehensive perioperative eye protection. *Braz J Anesthesiol*. 2021;71(6):595-598. doi:10.1016/j.bjane.2021.09.004
23. Figueredo CA, Abdelhay N, Figueredo CM, Catunda R, Gibson MP. The impact of vaping on periodontitis: a systematic review. *Clin Exp Dent Res*. 2021;7(3):376-384. doi:10.1002/cre2.360
24. Heller ZA, Ms ECA, Dmd JEP. Implications of electronic cigarettes on the safe administration of sedation and general anesthesia in the outpatient dental setting [published correction appears in Anesth Prog. 2022 Dec 1;69(4):50]. *Anesth Prog*. 2022;69(2):41-52. doi:10.2344/anpr-69-02-16
25. Bandara NA, Zhou XR, Alhamam A, Black PC, St-Laurent MP. The genitourinary impacts of electronic cigarette use: a systematic review of the literature [published online ahead of print, 2023 Jul 31]. *World J Urol*. 2023;10.1007/s00345-023-04546-1. doi:10.1007/s00345-023-04546-1
26. Feng M, Bai X, Thorpe AE, et al. Effect of e-vaping on kidney health in mice consuming a high-fat diet. *Nutrients*. 2023;15(14):3140. doi:10.3390/nu15143140
27. Nicholson T, Scott A, Newton Ede M, Jones SW. The impact of e-cigarette vaping and vapour constituents on bone health. *J Inflamm (Lond)*. 2021;18(1):16. doi:10.1186/s12950-021-00283-7
28. Nicholson T, Scott A, Newton Ede M, Jones SW. The impact of e-cigarette vaping and vapour constituents on bone health. *J Inflamm (Lond)*. 2021;18(1):16. doi:10.1186/s12950-021-00283-7
29. Flach S, Maniam P, Manickavasagam J. E-cigarettes and head and neck cancers: a systematic review of the current literature. *Clin Otolaryngol*. 2019;44(5):749-756. doi:10.1111/coa.13384
30. Bjurlin MA, Matulewicz RS, Roberts TR, et al. Carcinogen biomarkers in the urine of electronic cigarette users and implications for the development of bladder cancer: a systematic review. *Eur Urol Oncol*. 2021;4(5):766-783. doi:10.1016/j.euo.2020.02.004
31. Cao DJ, Aldy K, Hsu S, et al. Review of health consequences of electronic cigarettes and the outbreak of electronic cigarette, or vaping, product use-associated lung injury. *J Med Toxicol*. 2020;16(3):295-310. doi:10.1007/s13181-020-00772-w

32. Chaumont M, van de Borne P, Bernard A, et al. Fourth generation e-cigarette vaping induces transient lung inflammation and gas exchange disturbances: results from two randomized clinical trials. *Am J Physiol Lung Cell Mol Physiol*. 2019;316(5):L705-L719. doi:10.1152/ajplung.00492.2018
33. Song MA, Reisinger SA, Freudenheim JL, et al. Effects of electronic cigarette constituents on the human lung: a pilot clinical trial. *Cancer Prev Res (Phila)*. 2020;13(2):145-152. doi:10.1158/1940-6207.CAPR-19-0400
34. Effah F, Taiwo B, Baines D, Bailey A, Marczylo T. Pulmonary effects of e-liquid flavors: a systematic review. *J Toxicol Environ Health B Crit Rev*. 2022;25(7):343-371. doi:10.1080/10937404.2022.2124563
35. Martins BNFL, Normando AGC, Rodrigues-Fernandes CI, et al. Global frequency and epidemiological profile of electronic cigarette users: a systematic review. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2022;134(5):548-561. doi:10.1016/j.oooo.2022.07.019
36. Sharma A, McCausland K, Jancey J. Adolescent's health perceptions of e-cigarettes: a systematic review [published correction appears in Am J Prev Med. 2022 May;62(5):806]. *Am J Prev Med*. 2021;60(5):716-725. doi:10.1016/j.amepre.2020.12.013
37. Voos N, Kaiser L, Mahoney MC, et al. Randomized within-subject trial to evaluate smokers' initial perceptions, subjective effects and nicotine delivery across six vaporized nicotine products. *Addiction*. 2019;114(7):1236-1248. doi:10.1111/add.14602
38. Becker TD, Arnold MK, Ro V, Martin L, Rice TR. Systematic review of electronic cigarette use (vaping) and mental health comorbidity among adolescents and young adults. *Nicotine Tob Res*. 2021;23(3):415-425. doi:10.1093/ntr/ntaa171
39. Rothrock AN, Andris H, Swetland SB, et al. Association of e-cigarettes with adolescent alcohol use and binge drinking-drunkenness: a systematic review and meta-analysis. *Am J Drug Alcohol Abuse*. 2020;46(6):684-698. doi:10.1080/00952990.2020.1771723
40. Schaffer S, Strang A, Saul D, Krishnan V, Chidekel A. Adolescent e-cigarette or vaping use-associated lung injury in the delaware valley: a review of hospital-based presentation, management, and outcomes. *Cureus*. 2022;14(2):e21988. doi:10.7759/cureus.21988
41. Bourke M, Sharif N, Narayan O. Association between electronic cigarette use in children and adolescents and coughing a systematic review. *Pediatr Pulmonol*. 2021;56(10):3402-3409. doi:10.1002/ppul.25619
42. Li X, Zhang Y, Zhang R, Chen F, Shao L, Zhang L. Association between e-cigarettes and asthma in adolescents: a systematic review and meta-analysis. *Am J Prev Med*. 2022;62(6):953-960. doi:10.1016/j.amepre.2022.01.015
43. Lin SY, Wang L, Zhou W, Kitsantas P, Wen X, Xue H. E-cigarette use during pregnancy and its association with adverse birth outcomes in the US. *Prev Med*. 2023;166:107375. doi:10.1016/j.ypmed.2022.107375
44. Gaba M, Kumar N, Arumugam P, Dewan A. Vape-associated lung injury in immediate postoperative period: an upcoming perioperative respiratory risk factor. *BMJ Case Rep*. 2023;16(7):e255250. doi:10.1136/bcr-2023-255250
45. Maslonka MA, Schertz AR, Markowski LM, Miller PJ. Sedation challenges in patients with E-cigarette, or vaping, product use-associated lung injury (EVALI). *BMJ Case Rep*. 2020;13(9):e233866. doi:10.1136/bcr-2019-233866
46. Kalininskiy A, Bach CT, Nacca NE, et al. E-cigarette, or vaping, product use associated lung injury (EVALI): case series and diagnostic approach. *Lancet Respir Med*. 2019;7(12):1017-1026. doi:10.1016/S2213-2600(19)30415-1

47. Bizoń M, Maciejewski D, Kolonko J. E-cigarette or vaping product use-associated acute lung injury (EVALI) as a therapeutic problem in anaesthesiology and intensive care departments. *Anaesthesiol Intensive Ther*. 2020;52(3):219-225. doi:10.5114/ait.2020.97989
48. Rusy DA, Honkanen A, Landrigan-Ossar MF, et al. Vaping and e-cigarette use in children and adolescents: implications on perioperative care from the American Society of Anesthesiologists Committee on Pediatric Anesthesia, Society for Pediatric Anesthesia, and American Academy of Pediatrics Section on Anesthesiology and Pain Medicine. *Anesth Analg*. 2021;133(3):562-568. doi:10.1213/ANE.0000000000005519
49. Ashour O, Al-Huneidy L, Noordeen H. The implications of vaping on surgical wound healing: a systematic review. *Surgery*. 2023;173(6):1452-1462. doi:10.1016/j.surg.2023.02.017
50. Lynn RSR, Galinkin JL. Cannabis, e-cigarettes and anesthesia. *Curr Opin Anaesthesiol*. 2020;33(3):318-326. doi:10.1097/ACO.0000000000000872
51. Dudaryk R, Navas-Blanco JR, Eber ST, Epstein RH. Implementation of a preoperative screening tool to identify patients at risk for adverse perioperative pulmonary outcomes secondary to E-cigarette vaping: a pilot study. *J Clin Anesth*. 2020;66:109929. doi:10.1016/j.jclinane.2020.109929
52. Wong J, An D, Urman RD, et al. Society for Perioperative Assessment and Quality Improvement (SPAQI) consensus statement on perioperative smoking cessation. *Anesth Analg*. 2020;131(3):955-968. doi:10.1213/ANE.0000000000004508
53. Sameed M, Choi H, Auron M, Mireles-Cabodevila E. Preoperative pulmonary risk assessment. *Respir Care*. 2021;66(7):1150-1166. doi:10.4187/respcare.09154
54. Alasmari F, Crotty Alexander LE, Hammad AM, Bojanowski CM, Moshensky A, Sari Y. Effects of Chronic Inhalation of electronic cigarette vapor containing nicotine on neurotransmitters in the frontal cortex and striatum of C57BL/6 Mice. *Front Pharmacol*. 2019;10:885. doi:10.3389/fphar.2019.00885
55. Heldt NA, Seliga A, Winfield M, et al. Electronic cigarette exposure disrupts blood-brain barrier integrity and promotes neuroinflammation. *Brain Behav Immun*. 2020;88:363-380. doi:10.1016/j.bbi.2020.03.034
56. Munsamy A, Bhanprakash B, Sirkhot A, et al. A pre-test post-test assessment of non-invasive keratograph break up time and corneal epithelial thickness after vaping. *Afr Health Sci*. 2019;19(4):2926-2933. doi:10.4314/ahs.v19i4.13
57. Schwarzmeier LÂT, da Cruz BS, Ferreira CCP, Carvalho BFDC, Alves MGO, Lima Carta CF, Scholz JR, Almeida JD. E-cig might cause cell damage of oral mucosa. *Oral Surg Oral Med Oral Pathol Oral Radiol.* 2021 Apr;131(4):435-443. doi: 10.1016/j.oooo.2020.11.009. Epub 2020 Nov 19. PMID: 33610539.
58. Tommasi S, Caliri AW, Caceres A, Moreno DE, Li M, Chen Y, Siegmund KD, Besaratinia A. Deregulation of biologically significant genes and associated molecular pathways in the oral epithelium of electronic cigarette users. *Int J Mol Sci*. 2019 Feb 10;20(3):738. doi: 10.3390/ijms20030738.
59. Coppeta L, Magrini A, Pietroiusti A, Perrone S, Grana M. Effects of smoking electronic cigarettes on pulmonary function and environmental parameters. *Open Public Health J.* 2018 Aug 7;11:360-368. doi: 10.2174/1874944501811010360
60. Song MA, Reisinger SA, Freudenheim JL, Brasky TM, Mathé EA, McElroy JP, Nickerson QA, Weng DY, Wewers MD, Shields PG. Effects of electronic cigarette constituents on the human lung: a pilot clinical trial. *Cancer Prev Res* (Phila). 2020 Feb;13(2):145-152. doi:

10.1158/1940-6207.CAPR-19-0400. Epub 2019 Oct 16. PMID: 31619441; PMCID: PMC7007320.
61. Biondi-Zoccai G, Sciarretta S, Bullen C, et al. acute effects of heat-not-burn, electronic vaping, and traditional tobacco combustion cigarettes: The Sapienza University of Rome – vascular assessment of proatherosclerotic effects of Smoking (SUR-VAPES) 2 Randomized Trial. *J Am Heart Assoc*. 2019;8(6):e010455. doi:10.1161/JAHA.118.010455
62. Gonzalez JE, Cooke WH. Acute effects of electronic cigarettes on arterial pressure and peripheral sympathetic activity in young nonsmokers. *Am J Physiol Heart Circ Physiol*. 2021;320(1):H248-H255. doi:10.1152/ajpheart.00448.2020
63. Chaumont M, Tagliatti V, Channan EM, et al. Short halt in vaping modifies cardiorespiratory parameters and urine metabolome: a randomized trial. *Am J Physiol Lung Cell Mol Physiol*. 2020;318(2):L331-L344. doi:10.1152/ajplung.00268.2019
64. Ntima NO, Lumb AB. Pulmonary function tests in anaesthetic practice [published correction appears in *BJA Educ*. 2019 Nov;19(11):377]. *BJA Educ*. 2019;19(7):206-211. doi:10.1016/j.bjae.2019.02.001
65. Hemmings HC, Akabas MH, Goldstein PA, Trudell JR, Orser BA, & Harrison NL. Emerging molecular mechanisms of general anesthetic action. *Trends Pharmacol Sci*. 2019;40(10):773-789.
66. Alkire MT, Hudetz AG, Tononi G. Consciousness and anesthesia. *Science*. 2008;322(5903): 876-880.
67. Franks NP. General anaesthesia: from molecular targets to neuronal pathways of sleep and arousal. *Nat Rev Neurosci*. 2008;9(5):370-386.
68. Claassen JAHR, Thijssen DHJ, Panerai RB, Faraci FM. Regulation of cerebral blood flow in humans: physiology and clinical implications of autoregulation. *Physiol Rev*. 2021;101(4):1487-1559. doi:10.1152/physrev.00022.2020
69. Pang Y, Li Y, Zhang Y, et al. Effects of inflammation and oxidative stress on postoperative delirium in cardiac surgery. *Front Cardiovasc Med*. 2022;9:1049600. Published 2022 Nov 22. doi:10.3389/fcvm.2022.1049600
70. Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood–brain barrier. *Neurobiol Dis*. 2010;37(1):13-25.
71. Singh P, Tripathy K. *Keratopathy*. StatPearls Publishing; August 25, 2023.
72. Fraunfelder FT, Sciubba JJ, Mathers WD. The role of medications in causing dry eye [published correction appears in *J Ophthalmol.* 2019 Mar 4;2019:2989680]. *J Ophthalmol.* 2012;2012:285851. doi:10.1155/2012/285851
73. Kara-Junior N, Espindola RF, Valverde Filho J, Rosa CP, Ottoboni A, Silva ED. Ocular risk management in patients undergoing general anesthesia: an analysis of 39,431 surgeries. *Clinics*. 2015;70(8):541-543. doi:10.6061/clinics/2015(08)02
74. Hewson DW, Hardman JG. Physical injuries during anaesthesia. *BJA Educ.* 2018;18(10):310-316. doi:10.1016/j.bjae.2018.06.003
75. Burkat CN, Lucarelli, MJ. *Ophthalmology.* 2005;112:344-348.
76. Sridhar MS. Anatomy of cornea and ocular surface. *Indian J Ophthalmol.* 2018;66(2):190-194. doi:10.4103/ijo.IJO_646_17
77. Prineas S. Local and regional anesthesia for Ophthalmic Surgery. NYSORA. April 27, 2022. Accessed December 2, 2023. https://www.nysora.com/local-regional-anesthesia-ophthalmic-surgery/

78. Kelly DJ, Farrell SM. Physiology and role of intraocular pressure in contemporary anesthesia. *Anesth Analg.* 2018;126(5):1551-1562. doi:10.1213/ANE.0000000000002544
79. Bell A, Kasi A. Oral mucositis. StatPearls. July 1, 2023. Accessed December 2, 2023. https://www.ncbi.nlm.nih.gov/books/NBK565848/.
80. Politis C, Schoenaers J, Jacobs R, Agbaje JO. Wound healing problems in the mouth. *Front Physiol.* 2016;7:507. doi:10.3389/fphys.2016.00507
81. Hews J, El-Boghdadly K, Ahmad I. Difficult airway management for the anaesthetist. *Br J Hosp Med* (Lond). 2019;80(8):432-440. doi:10.12968/hmed.2019.80.8.432
82. Mathison M, Pepper T. Local anesthesia techniques in dentistry and oral surgery. StatPearls. June 1, 2023. Accessed December 2, 2023. https://www.ncbi.nlm.nih.gov/books/NBK580480/.
83. Park S, Oh EJ, Han S, et al. Intraoperative anesthetic management of patients with chronic obstructive pulmonary disease to decrease the risk of postoperative pulmonary complications after abdominal surgery. *Journal of Clinical Medicine.* 2020; 9(1):150. https://doi.org/10.3390/jcm9010150
84. Lemiere C, Lavoie G, Doyen V, Vandenplas O. Irritant-induced asthma. *J Allergy Clin Immunol Pract.* 2022;10(11):2799-2806. doi:10.1016/j.jaip.2022.06.045
85. Wesselink EM, Kappen TH, Torn HM, Slooter AJC, van Klei WA. Intraoperative hypotension and the risk of postoperative adverse outcomes: a systematic review. *Br J Anaesth.* 2018;121(4):706-721. doi:10.1016/j.bja.2018.04.036
86. Saugel B, Sessler DI. Perioperative blood pressure management. *Anesthesiology*. 2021;134(2):250-261. doi:10.1097/ALN.0000000000003610
87. Juri T, Suehiro K, Kanematsu R, et al. Validation of continuous noninvasive blood pressure monitoring using error grid analysis. *Anesth Analg*. 2022;134(4):773-780. doi:10.1213/ANE.0000000000005882
88. Knežević D, Ćurko-Cofek B, Batinac T, et al. Endothelial dysfunction in patients undergoing cardiac surgery: a narrative review and clinical implications. *J Cardiovasc Dev Dis.* 2023;10(5):213. doi:10.3390/jcdd10050213
89. Faraday N. Platelets, perioperative hemostasis, and anesthesia. *Anesthesiology*. 2002;96(5):1042-1043. doi:10.1097/00000542-200205000-00003
90. About MRH. About Us. Accessed November 25, 2023. https://www.mhs.net/about.
91. Electronic cigarette use among US adults, 2018. Centers for Disease Control and Prevention. April 30, 2020. Accessed August 29, 2023. https://www.cdc.gov/nchs/products/databriefs/db365.htm
92. More than 2.5 million youth reported e-cigarette use in 2022. Centers for Disease Control and Prevention. October 6, 2022. Accessed August 29, 2023. https://www.cdc.gov/media/releases/2022/p1007-e-cigarette-use.html
93. Moran KJ, Burson R, Conrad D. *The Doctor of Nursing Practice Project: A Framework for Success.* Jones & Bartlett Learning; 2020.
94. Bolarinwa OA. Sample size estimation for health and social science researchers: The principles and considerations for different study designs. *Niger Postgrad Med J*. 2020;27(2):67-75. doi:10.4103/npmj.npmj_19_20

Appendix A: Literature Review Characteristics Table

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
Alasmari F, Crotty Alexander LE, Hammad AM, Bojanowski CM, Moshensky A, Sari Y, 2019, Effects of Chronic Inhalation of Electronic Cigarette Vapor Containing Nicotine on Neurotransmitters in the Frontal Cortex and Striatum of C57BL/6 Mice	Design was quasi-experimental. The goal was to evaluate the concentrations of GABA in the frontal cortex and striatum of mice after long term exposure to EC vapors to determine whether the vapor induces any alterations in the inhibitory neuro-transmitter GABA and the excitatory neuro-transmitters dopamine and glutamate.	This experiment took place in the United States. EC liquid containing 50% glycerin, 50% propylene glycol, and 24mg/ml of nicotine were used for this project. Vapor was created by applying pneumatic pressure. 10 male C57BL/6 mice were placed in soft restraints where their noses were exposed and were made to inhale vapor for 4 seconds every 20 seconds for 1 hour per day for 5 days per	Independent variables: control group vs EC vapor group Dependent variables: Concentrations of glutamate, glutamine, GABA, dopamine, and serotonin in the frontal cortex and striatum	Unpaired independent *t*-test was used to analyze tissue content readings obtained for neurotransmitters of interest in the frontal cortex (FC) and striatum (STR). The level of significance was shown as $p < 0.05$.	When compared to the control group: Dopamine: EC group had lower concentrations in the STR but not the FC. Serotonin: No significant changes in either the FC or the STR. Glutamate: Significant increases in the STR but not the FC Glutamine: Significant increases in both the STR and FC GABA: Significant decreases in GABA in the FC but not in the STR	Chronic EC use induced changes in the neurochemical levels in the FC and STR.	Chronic daily inhalation of nicotine containing EC alters concentrations of neuro-transmitters within meso-corticolimbic brain regions, which may lead to addiction.	Level III evidence. Limitations of this study were small sample size, the species and gender specificity, the controlled exposure to conditions, the focus on specific neurotransmitters, exposure time, and lack of human correlation. This study provided evidence that changes occur in the brain when chronic use of ECs.

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		week for 6 months. The control group was placed in the same soft restraint but exposed to air. After 6 months, mice were euthanized, and their brains isolated. Tissue samples were taken to quantify the concentrations of glutamate, glutamine, GABA, dopamine, and serotonin.						
Heldt NA, Seliga A, Winfield M, et al. 2020. Electronic cigarette exposure disrupts blood-brain barrier integrity and promotes	Design was quasi-experimental. The goal was to determine the impact of long-term EC exposure on the blood brain barrier (BBB) function, expression of	This experiment took place in the United States. EC liquid contained nicotine concentrations of 0 or 18mg/mL. A 4 second puff	Independent variables: control group vs EC nicotine group vs cigarette group vs EC non-nicotine group Dependent variables: nicotine	All measures were expressed as mean with standard error of the mean. Shapiro-Wilk test was applied to test the data distribution. ANOVA was	Body weight and serum cotinine (biomarker of nicotine exposure): Cig exposed mice weighed less than other groups while neither EC group	EC emissions without nicotine had a robust effect that often exceeded the nicotine containing EC. This was particularly evident with respect to	Long-term use of ECs may negatively affect neurovascular health and contribute to cognitive dysfunction, regardless of nicotine content. EC	Level III evidence. Limitations of this study were the sample size and the inclusion of only male mice. The controlled laboratory conditions

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
neuroinflammation	vascular and inflammatory markers, permeability, leukocyte-endothelial interaction, and microglial activation. Affective state and cognitive function were also measured.	(~35mL) occurred every 30 seconds 2 hours per day, 5 days per week for 8 weeks. 2 cigarettes were burned concurrently for another group with 28 seconds interpuff duration. The control group was exposed to room air. Group sizes varied from 11-30 mice. Blood was collected at weeks 1, 3, 5, and 7 to determine nicotine and cotinine concentrations. Following euthanasia, lung, brain neocortex (frontal and	intake, tight junction and transporter associated mRNA expression, BBB permeability via tight junction proteins, pulmonary macrophages, microglial changes, and behavioral assessments	also used. The level of significance was shown as $p < 0.05$	impacted body weight. Cig and nicotine containing EC groups were in clinically relevant cotinine ranges supporting similar nicotine delivery. Genes associated with tight junction complexes responsible for the facilitation of drug efflux or active transport of key nutrients in relation to the BBB (Up/Down): cerebral microvessel mRNA showed significant upregulation and down-regulation in	reduced gene expression of critical BBB genes, increased paracellular permeability, and impaired cognition. All forms of EC and cig exposure impacted leukocyte margination with non-nicotine EC exhibiting the most robust response.	use is comparable to exposures of traditional cigarettes and may be uniquely deleterious in some contexts.	were also a limitation. This study also focused only on nicotine content and not the other ingredients found in ECs and traditional cigarettes that may contribute to these unique neurovascular effects.

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		parietal lobes), and basal ganglia were fixed for microglial analysis (brain) and total area excluding alveolar space (lung). Tracers and markers were injected just prior to euthanasia to determine BBB permeability. Plasma cytokine levels were determined via ELISA. Behavioral tasks were performed and measured throughout the experiment to determine ambulatory activity, anxiety-associated			the 0%EC (2163/2281), 1.8%EC (311/863), Cig (529/384). BBB immune associated genes: Cig exposure showed up regulation with a unique upregulation for 1.8%EC. BBB permeability: Expression of tight junction proteins for the BBB was significantly decreased in the cortex independent of nicotine when compared to room air. Similar trends were noted in the basal ganglia but did not approach significance. Tracers were			

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		behavior, and novel object recognition			also used to observe changes in permeability. Functional increases in permeability were unique to 0% EC exposure. Transporter protein Glut1 expression decreases following Cig exposure and EC regardless of nicotine content. Following tumor necrosis factor injection, leukocyte margination was elevated in all exposure groups when compared to room air, further supporting increased BBB permeability			

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
					for EC and cig groups. Pulmonary macrophages: Increased by exposure to nicotine containing EC or cigs. Neuro-inflammatory changes: No differences observed. Functional/ behavioral consequences: Data suggest a damaging effect of 0% EC on cognition (short-term memory and anxiety-related behavior).			
Md Isa NA, Koh PY, Doraj P, 2019, The Tear Function in Electronic Cigarette Smokers	Design was cross-sectional, single visit, pilot study. The goal was to determine dry eye symptoms,	This experiment took place in Malaysia. 42 participants with 21 in the control group of non-smokers and	Independent variables: control group of nonsmokers vs. vaping group Dependent variables:	Statistical analysis was performed using SPSS with intraclass correlation coefficient. Normality is assessed by	Overall, the vaping group experienced moderate to severe dry eyes. Break-up time in both noninvasive	The effect of vaping on dry eye symptoms and tear film integrity is very similar to that of tobacco cigarette smoking	When compared with nonsmokers, vapers experience moderate to severe eye dryness and their tear film	Level III evidence. Limitations were that this sample size was small, all male, and that this was a pilot study. More

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
	particularly tear film, between vapers and nonsmokers.	21 in the vaping group. Inclusion criteria were age 19-30 years with at least 1 year of vaping history at least 3mL/day with at least 50% propylene glycol liquid. Control group was healthy non-smokers. Ocular surface assessments started with noninvasive tear breakup (5 measurements taken and the 3 closest times were taken), followed by fluorescein breakup time slit lamp bio-microscopy; time interval for the first dark spot to appear after	ocular surface assessments 1. Noninvasive tear break-up 2. Fluorescein break-up time 3. Corneal staining 4. Tear meniscus height 5. Schirmer test	Shapiro-Wilk test ($p > 0.05$) and differences between groups were measured using independent *t*-test or Mann Whitney U test. Jonckheere-Terpstra test was used to identify trends from increased power output. Significance was determined at $p < 0.05$.	tear and fluorescein tests was significantly decreased in the vaping group. Tear volume/tear meniscus height was significantly decreased in the vaping group. Corneal staining was noted in 10 vapers and 4 nonsmokers at various locations (grade 1). Schirmer test showed a higher production of tears in vapers that was significant. With increasing power output/voltage on the vaping device,		function is significantly disturbed. There may be a counter-measure to combat these dry eye symptoms with over production of tears as confirmed by the Schirmer test. Interestingly, as power output from the device increased, the clinical parameters also significantly worsened.	studies should be done to confirm the results of this study

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		blinking, X3 measurements averaged), grading of corneal staining (done after fluorescein break up), tear meniscus height (image analysis, X3 measurements averaged), and then Schirmer test (length of wet strip after a period of time) for both eyes.			significance and values are significantly increased.			
Munsamy A, Bhanprakash B, Sirkhot A, et al, 2019, A pre-test post-test assessment of non-invasive keratograph break up time and corneal epithelial thickness after vaping	This was a quasi-experimental design with on group pretest and posttest. The goal was to determine the effect of vaping on the outer-most ocular surface, the corneal epithelium	This study was done in South Africa. 64 participants were originally admitted with reliable scans occurring for 58 participants; therefore, there were 58 eyes for corneal epithelial	Independent variables: Pre-test values Dependent variables: Post-test data	Data collection comprised of both pre-test and post-test measurements. Measurements were conducted by the same 2 examiners to ensure standardiz-ation. The corneal	Corneal Epithelial Thickness Analysis: The mean changes from pretest to posttest are central (-.3448 microns, p = 0.105), superior (-0.2414 microns, p = 0.230), inferior	While there is no statistical significance, there are increases seen in corneal thickness (central> inferior> temporal> superior> nasal) and increases in tear film	There are no statistically significant changes on the pretest and posttest when 10 puffs of EC are performed. Clinical increases were noted, which may be amplified with puff number	Level III evidence. The limitations of this study were that the sample size is limited, there was a lack of access to exclusive EC users, the inclusion of EC naïve subjects, and the influence

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
	with the use of corneal pachymetry and a non-invasive tear stability test.	thickness and 57 eyes for tear stability. Participants were recruited using a purposive sampling technique where the inclusion criteria were participants older than 18 years with no history of either acute or chronic systemic disease, history or presence of corneal disease, oculuar or systemic medications, recreational drug users, contact lens users, and persons who had undergone corneal		measurements were an average of 2 measurements while the first reading measurement for the average tear stability was analyzed using SPSS version 24. Statistical significance was given for $p < 0.05$.	(-0.2931 microns, p = 0.169), nasal (-0.2069 microns, p = 0.269), and temporal (-0.2759 microns, p = 0.117). None of these values showed statistical significance. Tear Film Stability Analysis: The average change was -1.40 seconds with p = 0.089. 41.1% had stable tear film post vaping, 42.8% had intermediate tear film post vaping, and 16.1% had unstable tear film post vaping.	instability when posttest values are compared to pretest values.	and repeated vaping throughout the day.	on corneal surface changes.

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		surgery. The effect of vaping on corneal epithelial thickness was measured using the Optovue iVue optical coherence tomographer pachymetry, and tear film stability was assessed using Non-Invasive Keratograph Break-Up Time with the Oculus keratography. Each participant was asked to vape 10 puffs of EC liquid of 8mg nicotine concentration (0.05mL of liquid) in a study site that was 4.67m by 2.25m with the						

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		air conditioning turned off.						
Schwarzmeier LÂT, da Cruz BS, Ferreira CCP, Carvalho BFDC, Alves MGO, Lima Carta CF, Scholz JR, Almeida JD., 2021, E-cig might cause cell damage of oral mucosa.	This was a quasi-experimental design where the focus was to investigate cytogenetic and cytotoxic damage through the evaluation of micronuclei and metanuclear anomalies frequency in the oral mucosa and of nicotine dependence in EC users compared with smokers of traditional cigarettes, former smokers, and nonsmokers.	This study took place in Brazil. 91 total participants split into 4 groups: nonsmokers, former smokers, EC users, and smokers. Inclusion criteria was absence of any history of oral malignancy and absence of any visible clinical signs of alteration at the site to be evaluated. Exclusion criteria were consumption of other forms of tobacco,	Independent: EC user vs. smoker vs. former smoker vs. control Dependent: CO concentration, Cotinine levels in the plasma, micronuclei levels, and metanuclear anomalies	Exploratory analyses were performed with the Kruskal-Wallis test with Dunn's test as a post-hoc method. Correlations and associations between data were determined using Spearman's correlation test and Fisher's exact test. Significance level of 5% was adopted for all tests.	Nicotine dependence/ICCS scores when compared across groups were non-significant ($p = 0.0296$). Smoking load was also non-significant ($p = 0.5069$). CO concentration was found to be significant ($P < .0001$). Plasma cotinine levels of the EC group were found to be non-significant when determining correlation to daily frequency ($p =$	Increased frequency of micronuclei, binucleation, broken egg, and nuclear bud are considered indicators of genotoxicity while karyolysis and karyorrhexis are indicators of cytotoxicity. Significantly higher number of broken eggs in the EC group than the smoker group and significantly more karyolysis, binucleation, broken eggs, and nuclear	The former smoker group showed no significant cytotoxicity, showing that there are benefits to quitting smoking and vaping altogether. While there are significant findings of cytotoxicity and genotoxicity in the oral mucosa cells in both the EC and smoking groups.	Level III evidence. The limitations of this article were that there was missing data in medical records, there was difficulty in standardizing the concentrations of EC liquid used, there was no scale for nicotine dependence, and there was a high incidence of alcohol use among participants.

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		any previous cancer treatment including surgery or radiotherapy/chemotherapy in any organ or system, and alteration of the oral mucosa. Evaluation of nicotine dependence was done by means of the ISCS score. The quantification of the smoking load was performed for the smoking group by calculation of pack years. Evaluation of cigarette consumption for the EC, smoker, former smoker groups were			0.213) and nicotine concentration found in EC liquid (p = 0.527). The frequency of micronuclei and metanuclear abnormalities in each group is presented graphically; Cells containing 1 micronucleus, total micro-nucleated cells, and total micronuclei were most frequent in the smoking group followed by the EC group and former smoker group and least frequent in the control group (p 0.0035, p = 0.0024, and p	buds than the former smoker and control groups.		

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		completed with CO concentration of exhaled air. Evaluation of plasma cotinine levels was also performed. Exfoliative cytology was performed of the lateral border of the tongue and mouth floor and then washed and fixed onto slides. Slides were evaluated for micronuclei and metanuclear abnormalities.			= 0.0014 respectively). The frequency of karyorrhexis, in order from most to least frequent was smoker group, EC group, former smokers, and nil for the control (p = 0.0028). The frequency of broken eggs in order from most to least frequent were EC users, smokers, and nil for former smokers or the control group. Karyolysis frequency from most to least frequent was EC users, smokers, and former smokers equaling the			

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
					control group (p = 0.0001). Binucleation frequency from most to least is as follows EC users, former smokers, smokers, and control group (p = 0.002). Nuclear budding frequency from most to least is as follows: EC group, smoking group, and nil for the former smokers and control group (p < 0.001). Qualitative variables assessed the frequency of micro-nuclei and metanuclear abnormalities for location			

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
					finding that there is a significant association in the EC and smoker groups for the tongue (p = 0.0098 and p = 0.26, respectively).			
Tommasi S, Caliri AW, Caceres A, Moreno DE, Li M, Chen Y, Siegmund KD, Besaratinia A., 2019, Deregulation of Biologically Significant Genes and Associated Molecular Pathways in the Oral Epithelium of Electronic Cigarette Users.	This is a blinded quasi-experimental study that sought to determine the effects of EC use vs. smoking on gene regulation by interrogating the oral transcriptome in the exclusive EC user and traditional cigarette smokers when compared to nonsmokers.	This study took place in the USA. 93 total participants split into EC users (n = 42), smokers (n = 24), and nonsmokers (n = 27) groups were used in this study. Individuals meeting criteria were contacted via phone and screened followed by an in-person interview for a second screening prior	Independent variables: EC users vs. smoking traditional cigarettes vs. nonsmokers Dependent variables: Changes in gene expression related to RNA sequencing, CO breath analysis, plasma cotinine results, and carboxyhemoglobin values.	Data analysis for gene ontology and canonical pathway was done using the database for annotation visualization and integrated discovery bioinformatics tool and the ingenuity pathway analysis tool.	Genome wide gene expression analysis: 857 upregulated transcripts and 295 down regulated transcripts in EC users and 1383 upregulated and 343 downregulated transcripts in smokers. (Smokers have nearly 50% more aberrantly expressed transcripts than EC users. Relative to	EC users have significant overexpression and under expression of genes in the oral epithelium, which is a major target site for smoking associated carcino-genesis. Diseases and disorders found to be genetically expressed in EC users are cancer, organismal injury/abnor-	Whole transcriptome analysis of oral cells from exclusive EC users and smokers shows that vapers, similarly to smokers, have deregulation of key genes, the majority of which converge on cancer related pathways and functions.	Level II evidence. The limitations of this study were that the sample size and composition is small, the exclusivity of EC vs. TC vs. nonsmoker groups, reliance of self-reported social habits, and variability in EC products.

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		to the study beginning. Exclusion criteria were oral infection or inflammation, gum disease, dental decay, immune system disorders, diabetes, respiratory disease, kidney disease, BMI < 18kg/m2 or > 40kg/m2, or any medical disorder or medication that could affect the study results or patient safety. Participants were asked to refrain from eating, smoking, or vaping at least 1 hour prior to lab collection. Participants			controls, both EC users and smokers are statistically significant differences for differentially expressed transcripts ($p <$ 0.005). Vape specific transcripts comprise of 74.1% of all differentially expressed transcripts in EC users, smoke specific transcripts constitute 82.7% of all transcripts in smokers. Gene ontology and molecular pathway/functi onal network analysis: Of the 1152 aberrantly expressed transcripts in	malities, neurologic disease, psychologic disease, and GI disease (Smokers = cancer, organismal injury and abnormalities, GI disease, dermatological diseases and conditions, and infectious diseases). Pathways effected by EC users are Wnt/Ca+ pathway, protein ubiquitation pathway, aryl hydrocarbon receptor signaling pathway, tRNA charging, and aldosterone signaling. (Smokers =		

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		were then asked to vigorously rinse their mouths with water to remove saliva, residual food particles, and mucosal debris. An ultra soft Oral-B brush with sufficient pressure was applied to contact the surface of the inside of the participants cheeks with rotatory motion along the face and edge of the brush was used to gently scrape the entire surface area of the inside of the cheek while avoiding bleeding.			EC users, 876 (76%) are connected to known disease processes while 1539/1726 deregulated transcripts in smokers (89%) are connected to known disease processes. 53% of aberrantly transcribed DNA sequences in EC users vs 79% in smokers were protein coding ($p < 0.0001$) and 28% of aberrant transcripts in EC users belonged to diverse classes of regulatory non-coding RNAs (in smokers this is	integrin signaling, phagosome maturation, insulin receptor signaling, ERK/MAPK signaling, and actin nucleation by ARP-WASP Complex).		

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		Proximal, central, and distal regions were brushed 15 times each. Plasma cotinine was measured and quantified via ELISA. CO levels in exhaled breath and percentage of carboxyhemoglobin were determined. Total RNA was isolated, sequenced, and analyzed to determine expression level of individual up regulated or down regulated genes.			about 8%) ($p <$ 0.0001). Most affected canonical pathway in EC users is the "Wnt/Ca+ pathway" while in smokers it is the "integrin signaling pathway". Pathways found to be affected by both smoking and EC use is the "Rho family of GTPases signaling pathway (number of downstream affected targets is 3X higher in smokers than vapers). Tumor suppressor p53 gene is the most			

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
					frequently mutated gene in the head and neck squamous cell carcinoma-associated with smoking. The most represented functional categories in EC users involved molecules that involved chaperones, stress response, and ATP-binding and Wnt-binding proteins (smokers = keratinocyte differentiation, small GTPase superfamily, cell to cell adhesion, and protein serine/threonine phosphatase activity).			

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
					Further noted analysis found that EC user gene ontology was commonly associated with tumorigenesis particularly in smoking related cancer (lung, squamous cell carcinoma of the head and neck, esophageal, bladder, ovarian, and leukemia.) (Smoking = cancer related and similar to EC users with potential to involve tumorigenesis initiation and promotion.)			

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
Coppeta L, Magrini A, Pietroiusti A, Perrone S, Grana M. 2018, Effects of smoking electronic cigarettes on pulmonary function and environmental parameters	Design was quasi-experimental. The goal is to assess whether the active use of ECs from healthy subjects can cause short term effects on lung function and if these changes are similar to tobacco smoke. The possible impact of environmental pollution was also measured.	This study took place in Italy. 17 men and 13 women (total 30) who were healthy (no history of chronic bronchopulmonary disease in the acute phase, respiratory allergies, respiratory symptoms, acute or chronic diseases regarding the cardiovascular system, liver, kidney, or urinary system, cancer, autoimmune, or immune-deficiency conditions, or pregnancy). Liquid used contained 1.8% nicotine	Independent values: baseline measurements Dependent values: Spirometry (onset of obstruction, changes in FEV1/FVC ratio, changes in FEV1, and changes in FEF 25-75) Environmental (emission assessment of nanoparticles at baseline, during smoking, and for 60 minutes post smoking session)	No sample size study was conducted before, and the data was analyzed with STAT 9 statistical package. Paired ANOVA test was used for statistical evaluation.	Pulmonary: In EC smokers, a significant decrease in FEV1 was observed 1 min after smoking but not at 15 minutes. A significant fall in FEV1/FVC ration and in FEF 25%-75% was observed after 1 minute. After 15 minutes post-exposure, a persistent decrease in FEF 25-75% but not FEV1/FVC was observed. Environ-mental: The average concentration of particles during and after smoking ECs was	5-minute use of EC caused a significant decrease in airflow when measured with flow-volume spirometry. No significant onset of obstruction patterns in exposed heathy volunteers. Trend of significant worsening of all respiratory parameters after 1 minute but not after 15 minutes from active EC smoking with a persistent decrease in FEF 25%-75%. Environmental study determined that aerosol generated by	The active use of EC by healthy subjects leads to worsening of the main parameters of ventilatory function after 5 minutes of exposure	Level III evidence. The limitations of this study were that there is a small sample size, a short duration of exposure with results examined for acute measurements, the lack of a control group, and the variability of ECs and TCs used.

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		(18mL/L), propylene glycol, glycerol, vegetable flavorings, and deionized water. Traditional cigarette contained 0.6mg nicotine, tar 8mg, and CO 9mg. Each participant underwent, on different days, a 5 minute session of active EC or traditional cigarette smoking. EC group was asked to perform 15 puffs of nicotine containing liquid with evaluations of spirometry			49690ppm/cm 3 (tobacco 42645pp/cm3) with the EC dropping to baseline values in 5 minutes and cigarette lasting for about 30 minutes.	EC falls within particle size similar to traditional cigarette and can pollute a closed environment for a short period of time (traditional cigarette pollutes much longer).		

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		occurring at baseline, within 1 min, and after 15 minutes.						
Song MA, Reisinger SA, Freudenheim JL, Brasky TM, Mathé EA, McElroy JP, Nickerson QA, Weng DY, Wewers MD, Shields PG., 2020, Effects of Electronic Cigarette Constituents on the Human Lung: A Pilot Clinical Trial.	Design was a randomized controlled trial. The goal is to better understand the health effects of ECs and focusing on the solvent carriers in EC liquid by conducting a clinical trial of never smokers randomized into nicotine and nicotine free EC use intervention groups and examining lung inflammation and gene expression.	This study took place in the United States. 30 never smokers between the ages of 21-30, without history of significant medical problems including lung disease, general anesthesia or bronchoscopy within the previous year, recent drug use, use of other combustible tobacco within the past year, pregnancy, or any other medical disorder that	Independent: non nicotine non flavor EC group vs control no intervention group Dependent: bronchial alveolar lavage cell counts and inflammatory cytokines, urinary propylene glycol analysis, and gene expression	Statistical analysis was performed using JMP 10 and Partek software. Data were summarized as mean and standard deviation with the Wilcoxon rank-sum test being used for associations and fisher's exact tests used for comparisons between intervention and control group.	Propylene glycol was significantly increased in the intervention group (p = 0.0015) but not the control group (p = 0.72). There were no significant differences in cell counts or cytokines between the control and intervention groups. Changes for these markers were correlated with changes in urinary propylene	EC use induced lung inflammation correlated with change in propylene glycol exposure. The use of nicotine and flavor free ECs did not affect gene expression, including expression commonly associated with cigarette smoking. Large magnitude changes in expression are likely not to occur from inhaling propylene glycol and	The data from this study provides direct safety information regarding the EC solvent carriers propylene glycol and vegetable glycerin. Small changes in inflammation correlated with change in propylene glycol exposure but no difference between the intervention and control groups in expression.	Level II evidence. The limitations of this study were the small sample size, the limited scope of EC liquid product, and the use of self-reporting and compliance.

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		would affect their bronchoscopy risk were selected. Pre-study broncho-scopies were performed on all subjects. One week after bronchoscopy, intervention participants were provided with an EC that contained 50% propylene glycol and 50% vegetable glycerin without nicotine or flavors and instructed to use the device at least twice per day, 20 puffs over 60 minutes. After 5 weeks, a second bronchoscopy was performed, 4			glycol levels as a marker of EC use and compliance. The intervention group was found to have statistically significant positive correlations of propylene glycol change with changes in total cell concentration (p = 0.03), lymphocyte counts (P = 0.02), and borderline significance in macrophage counts (p = 0.07). For controls, correlations were not statistically significant.	vegetable glycerin after 1 month of use.		

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		weeks of product use. Lung samples were collected by cronchial alveolar lavage for inflammatory cells and cytokines, and bronchial brushings from normal appearing epithelium for gene expression assays. Urine spot tests were also performed after 4 weeks of product use.			Change in propylene glycol was significantly correlated with changes in IL-8 (P= 0.02), IL-13 (P = 0.01), and TNF-α (P =0.01) for the intervention group but not the control group. There were no significant changes in gene expression from lung epithelial cell brushings for either group and no differences between the intervention and control groups.			

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
Biondi-Zoccai G, Sciarretta S, Bullen C, et al, 2019, Acute Effects of Heat-Not-Burn, Electronic Vaping, and Traditional Tobacco Combustion Cigarettes: The Sapienza University of Rome-Vascular Assessment of Proatheroscler otic Effects of Smoking (SUR - VAPES) 2 Randomized Trial	This study was an independent, randomized, crossover study. The aim was to compare heat-not-burn cigarettes (HNBC) vs ECs vs traditional cigarettes (TC) on several acute cardiovascular parameters: oxidative stress, flow mediated vascular dilation, platelet aggregation, blood pressure, and satisfaction.	This study was done in Italy. 20 healthy subjects with no acute or chronic organic, metabolic, and inflammatory disease or no fever/infection within 3 months, no cardiovascular symptoms, no allergies, and normal blood pressure levels and heart rhythm at screening were used for this study. Participants were all asked to smoke a single TC (average nicotine content 0.60mg), vaped 9 puffs from tobacco flavored EC	Independent: Baseline values taken from each participant prior to smoking sessions Dependent: values obtained after smoking sessions of markers of oxidative stress, antioxidant reserve, platelet function, and cotinine levels. Endothelial dysfunction and cardiovascular parameters	Variables were reported as means with standard deviation as percentages. Multilevel mixed effects linear model with identity covariance matrix was used for all findings. Nonparametric analyses with Wilcoxon signed ranks tests were done for satisfaction scores. Statistical significance was assigned by 2-tailed 0.05 level without multiplicity adjustment.	Oxidative stress profile: 3 markers of oxidative stress (sNox2-dp, productions of H2O2, and 8-iso-PGF2α) significantly increased following smoking of all devices (TC > EC > HNBC). Antioxidant Status: 2 indicators of antioxidant system effectiveness (vitamin E and hydrogen peroxide breakdown assay (HBA)) were measured with significant decreases in both the EC and TC groups with vitamin E	Use of any of these products is associated with acute detrimental effects on oxidative stress, antioxidant reserve, platelet function, flow mediated dilation, and blood pressure. Of note, with the HNBC and EC there are less detrimental effects than traditional cigarettes however their impact is still significant to health parameters.	Use of HNB, EC, or traditional cigarettes with equivalent nicotine consumption in a group of healthy adults was associated with acute multidimensio nal adverse effects on a range of biological and physiological markers. The HNB device is less impactful than both EV and traditional cigarettes.	Level I evidence. The limitations of this study were the small sample size, focus on specific health outcomes, the focus on specific health outcomes, the limited range of products tested the self-reported smoking history, the limited range of products tested, and the controlled nature of the setting.

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
		(average nicotine cartridge with 16mg at 250 puffs), or the HNBC (0.58mg nicotine in 9 puffs) over the course of 3 weeks with blood samples being drawn before and immediately after each product.			and no changes to the HNBC group. Significant decreases were noted for all groups however the EC and TC groups showed larger significance. Platelet Activation: 2 markers of platelet activation were measured (sCD40L and soluble P-selectin). All groups were found to have significant increases following smoking. Endothelial Dysfunction: 3 parameters were evaluated;			

Citation	Design/ Method	Sample/ Setting	Major Variables Studied and their Definitions	Measurement and Data Analysis	Findings	Results	Conclusions	Appraisal: Worth to Practice/Level
					flow mediated dilation, nitric oxide bioavailability, and blood pressure. Flow mediated dilation analysis showed a significant reduction after use of each device. Blood pressure parameters (SBP, DBP, and MAP) were significantly higher for all groups following smoking with a significant decrease in NO bioavailability being noted in the TC and EC groups. No changes were noted in the HNBC group.			

Appendix B: IRB Exemption

FIU | FLORIDA INTERNATIONAL UNIVERSITY

Office of Research Integrity
Research Compliance, MARC 430

MEMORANDUM

To:	Dr. Charles Buscemi
CC:	Lindsey Bell
From:	Kourtney Wilson, MS, IRB Coordinator KMW
Date:	February 6, 2024
Protocol Title:	"The Anesthetic Implications for the Patient who Vapes: A Quality Improvement Project"

The Florida International University Office of Research Integrity has reviewed your research study for the use of human subjects and deemed it Exempt via the **Exempt Review** process.

IRB Protocol Exemption #: IRB-24-0045 **IRB Exemption Date:** 02/06/24
TOPAZ Reference #: 113942

As a requirement of IRB Exemption you are required to:

1) Submit an IRB Exempt Amendment Form for all proposed additions or changes in the procedures involving human subjects. All additions and changes must be reviewed and approved prior to implementation.
2) Promptly submit an IRB Exempt Event Report Form for every serious or unusual or unanticipated adverse event, problems with the rights or welfare of the human subjects, and/or deviations from the approved protocol.
3) Submit an IRB Exempt Project Completion Report Form when the study is finished or discontinued.

Special Conditions: N/A

For further information, you may visit the IRB website at http://research.fiu.edu/irb.

KMW

Appendix C: QI Project Consent

FIU | FLORIDA INTERNATIONAL UNIVERSITY

CONSENT TO PARTICIPATE IN A QUALITY IMPROVEMENT PROJECT

Anesthetic Implications for the Patient who Vapes

SUMMARY INFORMATION

Things you should know about this study:

- **Purpose:** Educational module to increase providers awareness of the health hazards associated with the use of electronic cigarettes and the implications one should consider as an anesthesia provider in the perioperative period caring for the patient who vapes.
- **Procedures**: If the participant chooses to participate, they will be asked to complete a pretest, watch a voice PowerPoint, and then a post test
- **Duration:** This will take about a total of 30 minutes total.
- **Risks**: There will be minimal risks involved with this project, as would be expected in any type of educational intervention, which may include mild emotional stress or mild physical discomfort from sitting on a chair for an extended period.
- **Benefits:** The main benefit to you from this research is increase the participants knowledge on the anesthetic implications for the patient who vapes.
- **Alternatives:** There are no known alternatives available to the participant other than not taking part in this quality improvement project.
- **Participation:** Taking part in this quality improvement project is voluntary.

Please carefully read the entire document before agreeing to participate.

NUMBER OF STUDY PARTICIPANTS:

If the participant decides to be in this study, they will be one of approximately 10-15 people in this research study.

PURPOSE OF THE PROJECT

The participant is being asked to be in a quality improvement project. The goal of this project is to increase providers' knowledge on the health hazards associated with the use of electronic cigarettes and the anesthetic implications in the perioperative period for the patient who vapes. If you decide to participate, you will be 1 of approximately 10-15 participants.

DURATION OF THE PROJECT

The participation will require about 30 minutes

PROCEDURES

If the participant agrees to be in the project, PI will ask you to do the following things:
1. Complete an online 10 question pre-test survey via Qualtrics lasting 5 minutes, an Online survey product for which the URL link is provided.
2. Review the educational PowerPoint Module lasting 20 minutes via Qualtrics, an Online survey product

for which the URL link is provided.
3. Complete the online 10 question post-test survey via Qualtrics lasting 5 minutes, an Online survey product for which the URL link is provided.

RISKS AND/OR DISCOMFORTS
The main risk or discomfort from this research is minimal. There will be minimal risks involved with this project, as would be expected in any type of educational intervention, which may include mild emotional stress or mild physical discomfort from sitting on a chair for an extended period.

BENEFITS
The following benefits may be associated with participation in this project: Increased knowledge regarding the health hazards associated with the use of electronic cigarettes and the anesthetic implications in the perioperative period for the patient who vapes. The overall objective of the program is to increase the providers' knowledge based on the current literature.

ALTERNATIVES
There are no known alternatives available to the participant other than not taking part in this project. However, if the participant would like to receive the educational material, it will be provided to them at no cost.

CONFIDENTIALITY
The records of this project will be kept private and will be protected to the fullest extent provided by law. If, in any sort of report, PI might publish, it will not include any information that will make it possible to identify the participant. Records will be stored securely, and only the project team will have access to the records.

PARTICIPATION: Taking part in this quality improvement project is voluntary.

COMPENSATION & COSTS
There is no cost or payment to the participant for receiving the health education and/or for participating in this project.

RIGHT TO DECLINE OR WITHDRAW
The participation in this project is voluntary. The participant is free to participate in the project or withdraw the consent at any time during the project. The participant's withdrawal or lack of participation will not affect any benefits to which you are otherwise entitled. The investigator reserves the right to remove the participant without their consent at such time that they feel it is in their best interest.

RESEARCHER CONTACT INFORMATION
If you have any questions about the purpose, procedures, or any other issues relating to this research project, you may contact Lindsey Bell at 214.733.4774 or lbell083@fiu.edu and Dr. Charles Buscemi at 305-348-4870 or cbuscemi@fiu.edu.

IRB CONTACT INFORMATION

If the participant would like to talk with someone about their rights pertaining to being a subject in this project or about ethical issues with this project, the participant may contact the FIU Office of Research Integrity by phone at 305-348-2494 or by email at ori@fiu.edu.

PARTICIPANT AGREEMENT

I have read the information in this consent form and agree to participate in this study. I have had a chance to ask any questions I have about this study, and they have been answered for me. By clicking on the "consent to participate" button below I am providing my informed consent.

Appendix D: Recruitment Letter

Nicole Wertheim College of Nursing & Health Sciences

The Anesthetic Implications for the Patient who Vapes

Dear Memorial Regional Hospital Perioperative Providers:

My name is Lindsey Bell, and I am a student from the Anesthesiology Nursing Program Department of Nurse Anesthesiology at Florida International University. I am writing to invite you to participate in my quality improvement project. The goal of this project is to increase health care providers' awareness on the health hazards associated with the use of electronic cigarettes and the anesthetic implications in the perioperative period for the patient who vapes. You are eligible to take part in this project because you are a part of the Memorial Regional Hospital perioperative provider.

If you decide to participate in this project, you will be asked to complete and sign a consent form for participation. Next, you will complete a pre-test questionnaire, which is expected to take approximately 5 minutes. You will then be asked to view an approximately 20 minutes long educational presentation online. After going through the educational module, you will be asked to complete the post-test questionnaire, which is expected to take approximately 5 minutes. No compensation will be provided.

Remember, this is completely voluntary. You can choose to be in the study or not. If you'd like to participate or have any questions about the study, please email or contact me, Lindsey Bell at 214.733.4774 or lbell083@fiu.edu.

Thank you very much.

Sincerely,

Lindsey Bell
214.733.4774
lbell083@fiu.edu

Appendix E: Pre-Test/Post-Test

FIU | FLORIDA INTERNATIONAL UNIVERSITY

Pretest and Posttest Questionnaire:

THE ANESTHETIC IMPLICATIONS FOR THE PATIENT WHO VAPES

INTRODUCTION

The primary aim of this QI project is to increase providers on the health hazards associated with the use of electronic cigarettes and the anesthetic implications in the perioperative period for the patient who vapes

Please answer the question below to the best of your ability. The questions are either in multiple choice or true/false format and are meant to measure knowledge the health hazards associated with the use of electronic cigarettes and the anesthetic implications in the perioperative period for the patient who vapes.

PERSONAL INFORMATION

1. **Gender:** Male Female Other_____
2. **Ages 25 and above:** _____
3. **Ethnicity:** Hispanic Caucasian African American Asian Other_____
4. **Position/Title:** CRNA Anesthesiologist Resident Anesthesiologist Assistant
5. **Level of Education:** Certificate Bachelors Masters DNP PhD MD DO
6. How many years have you been a perioperative provider?

Over 10 5-10 years 2-5 years 1-2 years

QUESTIONNAIRE

1. **What is the estimated number of adults and adolescents in the United States who use Electronic Cigarettes?**
    a. **1 million**
    b. **5 million**
    c. **10 million**
    d. **15 million**
2. **Which of the following complications or poor patient outcomes can occur when patients undergo anesthesia without the anesthesia provider knowing their vaping history?**
    a. **EVALI (Electronic Cigarette or Vaping Associated Lung Injury)**
    b. **Sepsis**
    c. **Delayed wound healing**
    d. **All of the above**
3. **Which of the following neurotransmitter derangements is correct for the patient who vapes?**
    a. **↓ Serotonin**
    b. **↓ GABA**
    c. **↑ Dopamine**
    d. **↑ Acetylcholine**

4. **Which of the following are anesthetic implications for the neurological system for the patient who vapes?**
    a. **Increased risk for intraoperative awareness**
    b. **BBB disruption**
    c. **Decreased BIS monitoring effectiveness**
    d. **No significant effects**
5. **Which of the following are anesthetic implications for the ocular system for the patient who vapes?**
    a. **Increased tear production**
    b. **Increased risk for cataracts**
    c. **Increased risk for eye infection**
    d. **No significant effects**
6. **Which of the following are anesthetic implications for the oropharyngeal system for the patient who vapes?**
    a. **Decreased saliva production**
    b. **Increased risk for uvular necrosis**
    c. **Increased plaque build up**
    d. **No significant effects**
7. **Which of the following are anesthetic implications for the pulmonary system for the patient who vapes?**
    a. **Increased risk for upper airway infections**
    b. **Increased risk for reactive airway**
    c. **Maintain O2 saturations at 88-92%**

d. No significant effects

8. Which of the following are anesthetic implications for the cardiovascular system for the patient who vapes?

a. Hypotension

b. Bradycardia

c. Increased risk for vasospasms

d. No significant effects

9. Which of the following are anesthetic implications for the nicotine withdrawal for the patient who vapes?

a. Increased pain sensitivity

b. Postoperative delirium

c. Increased anxiolytic requirements

d. No significant effects

10. Your patient in the preoperative area admits they vape. Which of the following Electronic Cigarette flavors are you most worried about due to increase airway hyperresponsiveness?

a. Chocolate

b. Tobacco

c. Menthol

d. Mango

Appendix F: QI Educational Module

THE ANESTHETIC IMPLICATIONS FOR THE PATIENT WHO VAPES

Lindsey Bell, MSN, APRN, AGACNP-BC, FNP-BC

OBJECTIVES

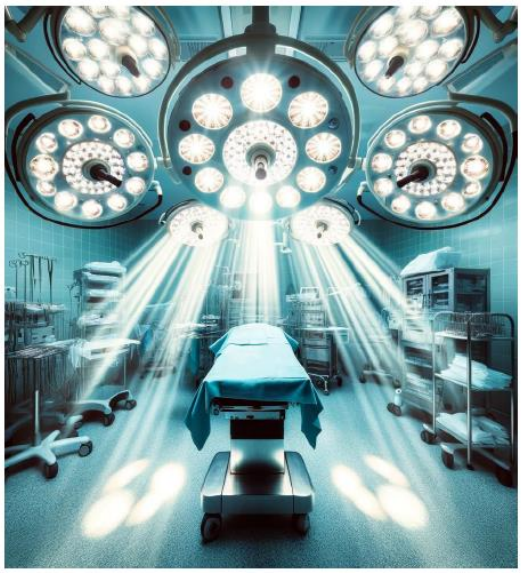
- Evaluate the health hazards associated with the use of electronic cigarettes (EC)
- Discuss anesthetic techniques to consider to avoid complications during the perioperative period
- Identify ways to assess a patient's risk for perioperative complications

BACKGROUND

- In the United States, 8.1 million adults and 2.55 million adolescents use ECs
- Evolution of EC design has newer generations containing low-resistance coils that allow for larger vapor clouds and increased administration of substances contained in the liquid
- Newer generations are marketed in bright colors with fun patterns or interesting shapes that are much smaller and easier to conceal than previous generations
- The additives in EC liquid are made to taste like a sweet treat that not only carries names and flavors that may be appealing to the adolescent population, but also can cause irreversible damage to the lungs and other organ systems
- Targeted consumers are vulnerable and are experiencing acute and chronic health problems associated with use
- In 2020, the Center for Disease Control (CDC) was forced to declare an outbreak of Electronic Cigarette or Vaping Associated Lung Injury (EVALI)

SCOPE OF THE PROBLEM

- Misconception among adolescents and young adults is that it is a healthier alternative to traditional cigarettes
- The degree and acceleration at which life-threatening lung injury is occurring in the adolescent population is increasing



CONSEQUENCES OF THE PROBLEM

- The detrimental effects of undergoing anesthesia without previous knowledge of vaping history can lead to complications and poor patient outcomes.
  - EVALI
  - Delayed wound healing
  - Sepsis
  - Misdiagnoses and delay of treatment
  - Inadequate anesthetic plane and medication interactions

SYSTEM BASED HEATH EFFECTS

NEUROLOGICAL

- Alterations in the concentration of excitatory and inhibitory neurotransmitters in the mesocorticolimbic brain regions
  - ↓ Dopamine
  - ↓GABA
  - ↑ Glutamine
  - ↑ Glutamate
- The long-term use of ECs can have adverse effects on neurovascular health and may contribute to cognitive dysfunction, regardless of nicotine content
  - This is due to the reduction in gene expression of critical blood brain barrier (BBB) genes, specifically expression of tight junction proteins for the BBB
- The effects of ECs may be equivalent to combustible traditional cigarettes (TCs) and have uniquely damaging properties for the neurological system

ANESTHETIC IMPLICATIONS: NEUROLOGICAL

- Dopamine, GABA, glutamate, and glutamine are important factors in maintaining consciousness and normal brain function.
  - These neurotransmitters also play a role in the induction of and emergence from general anesthesia
- Changes in neurotransmitter concentrations associated with EC use can increase the risk for:
  - Post Operative Nausea and Vomiting (PONV)
  - Increased requirements for sedatives due to increased neuronal excitability
  - Impact the effectiveness of commonly used medications in anesthesia
  - Delay emergence due to disturbances in neurotransmitter balance
- The damage to the neurovascular structures of the brain can significantly impact emergence.
- Neurovascular damage can lead to:
  - Impairment of cerebral autoregulation
  - Decreased cerebral reserve
  - Increased inflammation and oxidative stress
  - BBB disruption via tight junctions
  - Hemodynamic instability
- ECs can alter the penetration of drugs into the brain to further complicate emergence
- Exacerbation or increased risk for neurological injuries related to fluctuations in perfusion and oxygenation to the brain

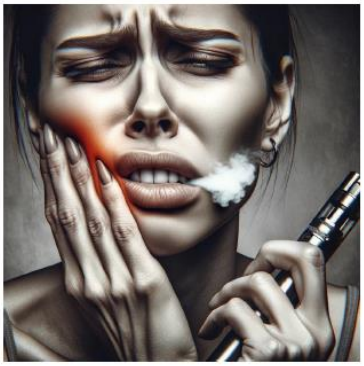
OCULAR

- Individuals who use ECs experience moderate to severe eye dryness and impaired tear film stability
  - Worsening of symptoms occurred with increases in EC device power output
- Changes to the integrity or thickness of the corneal surface associated with the use of ECs
  - Negative clinical trend, no significance

ANESTHETIC IMPLICATIONS: OCULAR

- Patients with unstable tear film and moderate to severe dry eye are at increased risk for corneal damage
- Commonly used anesthetic medications can worsen ocular symptoms and cause further damage
  - Anticholinergics
  - Opioids
- Overproduction of tears may provide a unique challenge during the intraoperative period
  - Distinguishing between natural tear production and injury
  - Trouble maintaining proper eye protection during extended surgical procedures
  - Recognizing the entry into phase 2 of anesthesia during the emergence process
- Increasing corneal thickness can alter the anatomy of the eye and the structures that surround and support it
  - Increased risk for injury
  - May affect the distribution of local anesthetic during a retrobulbar or peribulbar block
  - Changes in intraocular pressure
- Nicotine increases the risk for injury

OROPHARYNGEAL



- The use of ECs shows genotoxicity and cytotoxicity of oral mucosa cells
  - There is a need for further research
- Transcriptome analysis found that individuals who exclusively vape have changes in expression of key genes, similar to cigarette smokers
  - Tumor Suppressor Gene p53 is the most frequently mutated gene in the head and neck squamous cells
  - Upregulation of tumorigenesis genes known to cause cancer
    - Lung
    - Squamous cell carcinoma of the head and neck
    - Esophageal
    - Bladder
    - Ovarian
    - Leukemia
- Research is still needed to determine the long-term effects of passive exposure

ANESTHETIC IMPLICATIONS: OROPHARYNGEAL

- Patients who use ECs are at risk for impaired oral mucosa integrity
  - Impaired healing
  - Increased infection risk
  - The need for gentle airway management due to an enhanced inflammatory response
    - May require pretreatment with topical medications
    - May require the use of video laryngoscopy to avoid unanticipated trauma
- Increased difficulty with intubation with a need for advanced techniques to avoid unintentional damage
- Administration of anti-inflammatory agents to decrease the risk for post extubation swelling
- Regional anesthetic considerations for dental or oral surgery may not be appropriate and will require adjustment of anesthetic technique and plan of care
- Periodontal health decline with EC use
  - Plaque
  - Tooth decay
  - Bleeding in the oral cavity
- Components in vapor cause inflammation and disrupts normal oral flora
  - Tooth loss
  - Infection
  - Oropharyngeal cancer

PULMONARY

- After only 5 minutes of EC use, healthy individuals experience worsening ventilatory function that mimics an obstructive disease process.
  - ↓ FEV1
  - ↓ FEV1/FVC
  - ↓ FEF 25-75%
- Passive exposure and air quality studies show similarities to traditional cigarettes
- The ingredients found within the EC liquid have been found to cause inflammatory changes
  - Propylene glycol
  - Vegetable glycerin

ANESTHETIC IMPLICATIONS: PULMONARY

- Increased respiratory complications and challenges with ventilation
- Intraoperative management and emergence may be complicated
  - Optimize the patient to prevent negative outcomes
  - Continuous monitoring of oxygen saturation and end tidal CO2 with ABG analysis
- Prolonged emergence and delayed return of airway reflexes can occur
  - All objective criteria for extubation should be met
- Consider regional anesthesia to prevent complications
- Increased risk for inflammatory processes
  - Bronchospasms
  - Atelectasis
  - Laryngospasm
  - Carefully choose induction and volatile agents due to increased reactivity of the airway
- Consider treatment in preop for a reactive airway
  - Bronchodilators
  - Anticholinergics
  - Corticosteroids
- These anesthetic considerations may be warranted for patients who are passively exposed to ECs

CARDIOVASCULAR

- Acute detrimental effects on cardiovascular parameters with the use of ECs
  - ↑ Markers of oxidative stress
  - ↑ Markers of platelet activation
  - ↓ Indicators of antioxidant system effectiveness
  - Endothelial dysfunction
    - ↓ Flow mediated dilation
    - ↓ Nitric oxide bioavailability
- Hemodynamic parameters
  - ↑ Systolic blood pressure
  - ↑ Diastolic blood pressure
  - ↑ Mean arterial pressure
  - ↑ Heart rate
- Inhibition of muscle sympathetic nerve activity
- ↓ Baroreflex sensitivity

ANESTHETIC IMPLICATIONS: CARDIOVASCULAR

- Alterations in hemodynamics increase the risk for intraoperative complications
  - Myocardial infarction
  - Cardiac arrhythmias
  - Hemodynamic instability related to impaired baroreceptor response
- Consider advanced hemodynamic monitoring
- Careful fluid management
  - Maintain appropriate fluid balance to avoid large swings in hemodynamics
- ↑ Risk for thrombosis
  - Consider hematology consult with abnormal labs
- Nicotine withdrawal may occur
  - Preop: may manifest as ↑ levels of anxiety
  - Intraop: may manifest as ↑ heart rate and blood pressure
  - For surgical procedures that are long in duration, consider ↑ anxiolytics or nicotine replacement
- ↑ Risk for vasospasms due to endothelial dysfunction from derangements in oxidative stress and antioxidant status
  - Maintain stable hemodynamics and fluid status to avoid worsening endothelial dysfunction
  - Avoid use of nitrous oxide

PREOPERATIVE EVALUATION TECHNIQUES

- Quantification of use
  - Never
  - Former
  - Current
    - Consider determining the number of cartridges vaped per unit of time (daily, weekly, etc.)
- Type of EC liquid
  - Nicotine
  - Other additives
- Certain flavorings have significantly worse toxicity in the lungs
  - Reduced cell proliferation and increased airway hyperresponsiveness
    - Mint or menthol
    - Cinnamon
    - Strawberry
- Abstaining on the day of surgery

Neurological Effects

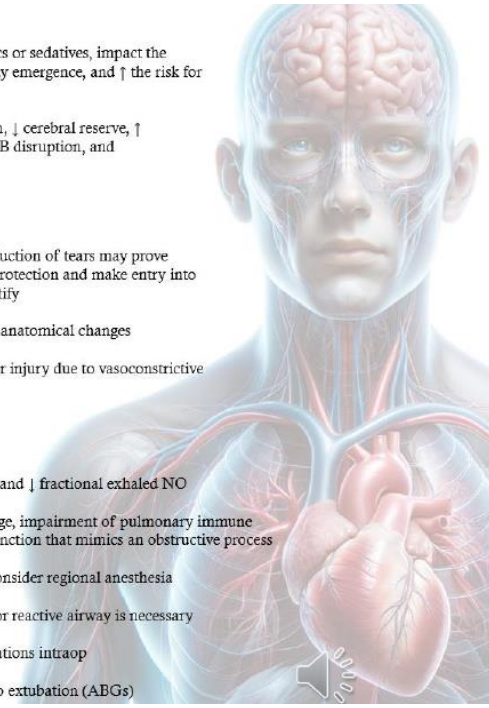
- ↑ PONV, ↑ requirements for anxiolytics or sedatives, impact the effectiveness of anesthetic agents, delay emergence, and ↑ the risk for emergence agitation.
- Impairment of cerebral autoregulation, ↓ cerebral reserve, ↑ inflammation and oxidative stress, BBB disruption, and hemodynamic instability

Ocular Effects

- ↑ Risk for corneal abrasions, overproduction of tears may prove troublesome maintaining proper eye protection and make entry into phase II of anesthesia difficult to identify
- Issues with regional anesthesia due to anatomical changes
- ↑ IOP, ↑ risk of nystagmus, and risk for injury due to vasoconstrictive effects of nicotine

Pulmonary Effects

- ↑ Airway resistance, ↓ O2 saturations, and ↓ fractional exhaled NO
- Interruption in pulmonary gas exchange, impairment of pulmonary immune function, and worsening ventilatory function that mimics an obstructive process
- ↑ Risk for reactive airway processes, consider regional anesthesia
- Determine if preoperative treatment for reactive airway is necessary
- Passive exposure may lead to complications intraop
- Consider advanced monitoring prior to extubation (ABGs)



Oropharyngeal Effects

- Impaired healing, ↑ infection risk, ↑ plaque, ↑ tooth decay or loss, and ↑ bleeding in the oral cavity
- ↑ Risk for oropharyngeal cancer
- Gentle airway management recommended with potential need for pretreatment with topical medications and use of video laryngoscopy
- Regional anesthetics may be inappropriate
- Administration of corticosteroids may be warranted prior to extubation to prevent post-extubation swelling

Cardiovascular Effects

- ↑ Risk for MI, cardiac arrhythmias, and unstable hemodynamics due to impaired baroreceptor response
- Advanced hemodynamic monitoring may be necessary
- Careful fluid management
- ↑ Risk for thrombosis due to ↑ platelet activation, consider a hematology consult with derangements in laboratory values
- Nicotine withdrawal may occur and cause unstable hemodynamics
- ↑ Risk for vasospasm due to endothelial dysfunction cause by ↑ oxidative stress and ↓ antioxidant status
- Consider avoiding N2O due to its association with worsening of endothelial status

18

REFERENCES

1. Carrick MA, Robson JM, Thomas C. Smoking and anaesthesia. BJA Educ. 2019;19(1):1-6. doi:10.1016/j.bjae.2018.09.005
2. Banks E, Yazidjoglou A, Brown S, et al. Electronic cigarettes and health outcomes: umbrella and systematic review of the global evidence. Med J Aust. 2023;218(6):267-275. doi:10.5694/mja2.51890
3. Electronic cigarettes. Centers for Disease Control and Prevention. July 12, 2021. Accessed August 29, 2023. https://www.cdc.gov/tobacco/basic_information/e-cigarettes/index.htm
4. Products - data briefs - number 365 - April 2020. Centers for Disease Control and Prevention. April 30, 2020. Accessed August 29, 2023. https://www.cdc.gov/nchs/products/databriefs/db365.htm
5. More than 2.5 million youth reported e-cigarette use in 2022. Centers for Disease Control and Prevention. October 6, 2022. Accessed August 29, 2023. https://www.cdc.gov/media/releases/2022/p1007-e-cigarette-use.html.
6. Overbeek DL, Kass AP, Chiel LE, Boyer EW, Casey AM. A review of toxic effects of electronic cigarettes/vaping in adolescents and young adults. Critical Reviews in Toxicology. 2020;50(6):531-538. doi:10.1080/10408444.2020.1794443
7. Ozgunay SE, Karasu D, Dulger S, Yilmaz C, Tabur Z. Relationship between cigarette smoking and the carbon monoxide concentration in the exhaled breath with perioperative respiratory complications. Braz J Anesthesiol. 2018;68(5):462-471. doi:10.1016/j.bjan.2018.02.006
8. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health. E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General. Atlanta (GA): Centers for Disease Control and Prevention (US); 2016.
9. Sharma A, McCausland K, Jancey J. Adolescent's Health Perceptions of E-Cigarettes: A Systematic Review [published correction appears in Am J Prev Med. 2022 May;62(5):806]. Am J Prev Med. 2021;60(5):716-725. doi:10.1016/j.amepre.2020.12.013
10. Voos N, Kaiser L, Mahoney MC, et al. Randomized within-subject trial to evaluate smokers' initial perceptions, subjective effects and nicotine delivery across six vaporized nicotine products. Addiction. 2019;114(7):1236-1248. doi:10.1111/add.14602
11. Schaffer S, Strang A, Saul D, Krishnan V, Chidekel A. Adolescent E-cigarette or Vaping Use-Associated Lung Injury in the Delaware Valley: A Review of Hospital-Based Presentation, Management, and Outcomes. Cureus. 2022;14(2):e21988. Published 2022 Feb 7. doi:10.7759/cureus.21988
12. Bourke M, Sharif N, Narayan O. Association between electronic cigarette use in children and adolescents and coughing a systematic review. Pediatr Pulmonol. 2021;56(10):3402-3409. doi:10.1002/ppul.25619
13. Li X, Zhang Y, Zhang R, Chen F, Shao L, Zhang L. Association Between E-Cigarettes and Asthma in Adolescents: A Systematic Review and Meta-Analysis. Am J Prev Med. 2022;62(6):953-960. doi:10.1016/j.amepre.2022.01.015
14. Gaba M, Kumar N, Arumugam P, Dewan A. Vape-associated lung injury in immediate postoperative period: an upcoming perioperative respiratory risk factor. BMJ Case Rep. 2023;16(7):e255250. Published 2023 Jul 11. doi:10.1136/bcr-2023-255250
15. Maslonka MA, Schertz AR, Markowski LM, Miller PJ. Sedation challenges in patients with E-cigarette, or vaping, product use-associated lung injury (EVALI). BMJ Case Rep. 2020;13(9):e233866. Published 2020 Sep 2. doi:10.1136/bcr-2019-233866
16. Kalininskiy A, Bach CT, Nacca NE, et al. E-cigarette, or vaping, product use associated lung injury (EVALI): case series and diagnostic approach. Lancet Respir Med. 2019;7(12):1017-1026. doi:10.1016/S2213-2600(19)30415-1
17. Bizoń M, Maciejewski D, Kolonko J. E-cigarette or vaping product use-associated acute lung injury (EVALI) as a therapeutic problem in anaesthesiology and Intensive care departments. Anaesthesiol Intensive Ther. 2020;52(3):219-225. doi:10.5114/ait.2020.97989
18. Ruoy DA, Honkanen A, Landrigan-Ossar MF, et al. Vaping and E-Cigarette Use in Children and Adolescents: Implications on Perioperative Care From the American Society of Anesthesiologists Committee on Pediatric Anesthesia, Society for Pediatric Anesthesia, and American Academy of Pediatrics Section on Anesthesiology and Pain Medicine. Anesth Analg. 2021;133(3):562-568. doi:10.1213/ANE.0000000000005519
19. Ashour O, Al-Huneidy L, Noordeen H. The implications of vaping on surgical wound healing: A systematic review. Surgery. 2023;173(6):1452-1462. doi:10.1016/j.surg.2023.02.017
20. Lynn RSR, Galinkin JL. Cannabis, e-cigarettes and anesthesia. Curr Opin Anaesthesiol. 2020;33(3):318-326. doi:10.1097/ACO.0000000000000872
21. Ali N, Xavier J, Engur M, Pv M, Bernardino de la Serna J. The impact of e-cigarette exposure on different organ systems: A review of recent evidence and future perspectives. J Hazard Mater. 2023;457:131828. doi:10.1016/j.jhazmat.2023.131828
22. Yingst J, Foulds J, Veldheer S, et al. Measurement of Electronic Cigarette Frequency of Use Among Smokers Participating in a Randomized Controlled Trial. Nicotine Tob Res. 2020;22(5):699-704. doi:10.1093/ntr/nty233
23. Duderyk R, Navas-Blanco JR, Eber ST, Epstein RH. Implementation of a preoperative screening tool to identify patients at risk for adverse perioperative pulmonary outcomes secondary to E-cigarette vaping: A pilot study. J Clin Anesth. 2020;66:109929. doi:10.1016/j.jclinane.2020.109929
24. Wong J, An D, Urman RD, et al. Society for Perioperative Assessment and Quality Improvement (SPAQI) Consensus Statement on Perioperative Smoking Cessation. Anesth Analg. 2020;131(3):955-968. doi:10.1213/ANE.0000000000004508
25. Sameed M, Choi H, Auron M, Mireles-Cabodevila E. Preoperative Pulmonary Risk Assessment. Respir Care. 2021;66(7):1150-1166. doi:10.4187/respcare.09154
26. Effah F, Taiwo B, Baines D, Bailey A, Marczylo T. Pulmonary effects of e-liquid flavors: a systematic review. J Toxicol Environ Health B Crit Rev. 2022;25(7):343-371. doi:10.1080/10937404.2022.2124563
27. Ruszkiewicz JA, Zhang Z, Gonçalves FM, Tizabi Y, Zelikoff JT, Aschner M. Neurotoxicity of e-cigarettes. Food Chem Toxicol. 2020;138:111245. doi:10.1016/j.fct.2020.111245
28. 28. Cascella M, Bimonte S, Muzio MR. Towards a better understanding of anesthesia emergence mechanisms: Research and clinical implications. World J Methodol. 2018;8(2):9-16. Published 2018 Oct 12. doi:10.5662/wjm.v8.i2.9