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Abstract

In August 2019 an unexplained, exponential rise in severe respiratory illnesses in previously healthy young adults, swept across America catching the attention of medical providers. Hospital admissions for lung injury increased 10-fold over two months' time leaving practitioners scrambling for answers. All affected patients were found to have used e-cigarettes prior to symptoms and endorsed using nicotine and marijuana vape pens. The medical community quickly began to search for the cause of these vaping associated lung injuries. Understanding the mechanism of injury is important in order to assist in educating the public about the risks associated with e-cigarettes. The aim of this paper is to present the research, or lack thereof, surrounding the risks of electronic cigarettes and their association with severe lung injury. A thorough literature review was performed eliciting 12 appropriate studies. A conclusive causative agent for EVALI has not been identified but several possible culprits are Vitamin E Acetate, propylene glycol or glycerol and metal nanoparticles. Recommendations for future research, provider and patient education and policy change are provided.

Keywords: vaping, e-cigarettes, adolescents, cannabis, cannabidiol, lung injury, lung disease

A Search for the Cause of Vaping Associated Lung Injury in Adolescents

In the late summer months of 2019, the Centers for Disease Control were inundated with reports of severe lung disease in previously healthy adolescents and youth. Through chart review and interview, the common denominator between all ill patients was the use of e-cigarettes. E-cigarettes, or vapes, are part of a $2.5 billion-dollar industry (Truth Initiative, 2019). Like cigarettes of the past, there is rising concern that e-cigarette companies are targeted adolescents through marketing strategies and by adding flavors to create nicotine addicts at a young age.

In addition to this concern, increasing number of adolescents are vaping other substances, particularly cannabis products including tetrahydrocannabinol (THC) and cannabidiol (CBD). The combination of e cigarettes and marijuana was 'all but inevitable,' (Poklis, 2019, p. e25), but the repercussion of this combination was not anticipated. As legalization of marijuana continues to gain traction, it is expected that there will be an increase in the amount of marijuana that is vaped. With anticipation of this, providers should be knowledgeable about the causes of vaping associated lung injury and well versed in the risks associated with vaping. This literature review will attempt to identify the best evidence associated with vaping associated lung injury in adolescents and inform the professional recommendations.

Background

E-cigarettes were first introduced to the market in 2007. A major concern around electronic cigarettes has been inappropriate marketing. For years, there has been concern throughout the medical community regarding the lack of research to support claims that e-cigarettes are a safer alternative to traditional smoking. While still addictive, these devices have been marketed as healthier alternatives since they decrease the amount of inhaled toxic smoke compared to combustible cigarettes (Budney, et al., 2015). This claimed benefit of vaping is

proposed to be due to the inhalation of aerosol liquids with fewer chemicals than the thousands found in cigarette smoke (Palazzolo, 2013). Unfortunately, these claims may be false due to the higher numbers of chemicals in vaping solution than originally thought, and lack of longitudinal studies to address the effects of long-term vaping (Budney, et al., 2015). Moreover, even though ingredients used in e-cigarettes have been deemed safe by the Food and Drug Administration (FDA) for consumption but many of them have not been approved for inhalation (Truth Initiative, 2019).

Combustible cigarettes are the leading cause of preventable deaths in the United States so finding products to aid in smoking cessation is imperative (Truth Initiative, 2019). E-cigarette companies took advantage of this notion and initially promoted themselves as smoking alternatives. In response to this, the FDA sent warning letters since these claims were not based in fact or supported by research. In fact, the FDA recommended that e-cigarettes be labeled as dangerous nicotine delivery devices that should be regulated by the Federal Food Drug and Cosmetic Act (Palazzolo, 2013). After numerous rounds of legal battles, the US Court of Appeals stated that e-cigarettes must be marketed as a smokeless tobacco product (even though they contain trace amounts of tobacco and smoke) and cannot be marketed as smoking cessation aides or a healthier option until research could support these claims (Palazzolo, 2013).

These devices quickly evolved to include nicotine, THC, CBD, and flavorings to make them more appealing to consumers. Various types of e-cigarettes are available with the newest generation of vape pens being created by JUUL in 2015. These pens are sleek, reusable, and easily rechargeable. JUUL quickly became the number one e-cigarette company supplying over three-quarters of the market (Truth Initiative, 2019).

The term vaping refers to the inhalation of a combination of propylene glycol, active ingredients (i.e. nicotine or THC), water and flavorings that have been vaporized (Budney, Sargent & Lee, 2015). Through this process, the desired liquid, as well as biproducts from the device, are inhaled. With legislation pushing for increased legalization of marijuana, vaping THC will continue to rise (Budney, Sargent & Lee, 2015). Healthcare providers must be informed about vaping and the associated health consequences as use continues to climb with over nine million adults using e-cigarettes with nicotine or other substances (Truth Initiative, 2019).

In the summer of 2019, healthcare providers noted an abrupt increase in severe respiratory symptoms in adolescents and young adults. These individuals (average age of 24 years) had an acute onset of respiratory distress leading to lipoid pneumonia, acute respiratory distress syndrome and even death (Moritz, et al., 2019). Through careful review, pulmonologists and cricial care physicians identified the common denominator between these patients was vaping. Therefore, these individuals were diagnosed with electronic-cigarette or vaping associated lung injury (EVALI). This outbreak lead to 2,807 hospitalized cases and 68 deaths among all 50 states (Truth Initiative, 2019).

Vaping has been around since 2009 with minimal serious side effects. So, what caused this significant uptick in cases requiring hospitalization and killing otherwise healthy young people? Throughout the outbreak hypotheses poured in regarding possible contaminations or toxins that could be the culprit. A theory that had gained support was the idea that vaping marijuana along with the associated additives was the cause of these symptoms. As a result, the Centers for Disease Control and Prevention (CDC) recommended cessation of vaping marijuana and to vape other substances with caution until a causative agent could be identified (Siegel, et

al., 2019). Therefore, the clinical question guiding this paper is as follows: *Are adolescents who vape cannabis (or cannabinoids) at increased risk for lung disease or injury compared with those who do not vape cannabis?*

Methods

Beginning on October 10, 2019, an extensive literary search began utilizing various databases selected for their content and accessibility. The search concluded on November 12, 2019. The databases utilized included CINAHL, MEDLINE (PubMed), Cochrane, Academic Search Premier, and Nursing and Allied Health Database. Searches were limited by the following criteria: full-text, peer reviewed, and published between 2015 and 2019 (see Table 1of the Appendix for general subjects covered by each selected database). Search terms were variations of the original clinical question and included "vaping," e-cigarettes," "vaping cannabis," "cannabidiol," "lung injury," "lung disease," "adolescents," and "teens." All searches that yielded less than 100 results were reviewed for relevance and applicability to the clinical question. Refer to Table 2 in the Appendix for search results broken down by search terms and databases. After review of all search combinations and databases, 72 articles were included for further review. Articles were chosen after reviewing abstracts for applicability to the clinical question.

Articles that pertained to the outbreak of lung disease in late 2019 were included. Articles that discussed the pathophysiology of lung injury, possible causative agents of lung injury and interim guidelines were included. Articles discussing various types of vaporized marijuana products including THC and CBD, and possible contaminants were included. Articles that compared vaping to cigarette use were excluded. Articles which compared vaporized nicotine to

non-nicotine containing e-cigarettes were excluded. See Table 3 in Appendix for a detailed summary of the articles included or excluded along with the rationale.

The 12 studies that met inclusion criteria were reread and analyzed to identify key findings that will affect practice and level of evidence. The levels of evidence (Melnyk and Fineout-Overholt, 2015) ranged from Level II-Level VII (1 Level II, 2 Level III, 2 Level IV, 2 Level V, 1 Level VI, and 4 Level VII). Among the varying levels of evidence there was a combination of randomized control trial reviews, single cohort/case studies, laboratory studies, and expert opinions. The limited number of high-quality research articles was mentioned by authors of several articles further identifying a need for increased research into EVALI. Description of studies with associated findings and level of evidence can be found in Table 4 of the Appendix.

Literature Review

With their introduction to the market in 2007, e-cigarettes had a level of speculation from the beginning. Promoted as a safer alternative to combustible cigarettes, critics were quick to notice a lack of research to support these claims. Electronic cigarette companies proposed that their products were healthier since consumers were inhaling lower number of chemicals when compared to cigarette smoke (Budney, et al., 2015). While this is a potential benefit as many of the ingredients in vaping solution are deemed safe for consumption by the FDA, there are no longitudinal studies on the long-term effects of inhaling these chemicals has on lung tissue and overall health (Budney, et al., 2015). Budney, Sargent and Lee (2015) referred to electronic cigarettes as a “double-edged sword” where practitioners must outweigh the potential, unknown risk with the benefit of working towards smoking cessation.

Palazzolo and colleagues (2013) had similar concerns with the lack of scientific research to support e-cigarette company's health claims. Through a literature review, the researchers found that vaping was "as effective" as other FDA approved nicotine replacement therapies, such as registered Nicotrol inhalers (Palazzolo, et al., 2013). These claims mean that companies cannot market electronic cigarettes as healthier options. In 2010, the US Court of Appeals deemed these products must be labeled as dangerous nicotine delivery device and marketing must not be directed at minors (Palazzolo, et al., 2013).

Electronic cigarette designs have changed immensely since their consumption and now are discrete and difficult to identify. This feature has led to the increasing use of electronic cigarettes in non-smoking areas and threatening anti-smoking initiatives (Truth Initiative, 2020). Additionally, there is fear that electronic cigarettes are geared towards a new generation of potential nicotine addicts (Palazzolo, et al., 2015). This again presents electronic cigarettes as a double-edged sword: will they decrease the amount of combustible cigarettes consumed while increasing rates of new and younger electronic cigarette users (Palazzolo, et al., 2015)?

The difficult situation for providers is the risk management in patients. Combustible cigarettes are the leading cause of preventable death in the United States, so action is needed to combat this epidemic (Palazzolo, et al., 2015). Without longitudinal studies, providers cannot accurately state that there will not be long-term health effects on these young patients (Budney, Sargent & Lee, 2015). Researchers feared that the lack of research would lead to deleterious outcomes for consumers. Unfortunately, this fear came true in the summer of 2019.

Providers in numerous states began reporting numerous cases of severe, respiratory symptoms in young patients. Patients initially presented with vague symptoms of low-grade fevers, tachypnea, dyspnea, hypoxia with oxygen saturations less than 90% of room air, nausea,

vomiting and abdominal discomfort (Davidson, et al., 2019). Clinicians were confounded by these debilitating symptoms that lasted for several weeks in young adults. Searching for a cause, data was compiled at the CDC and the Lung Injury Response Clinical Working Group was created (Siegel, et al., 2019). This group consisted of nine practitioners leading the field in pulmonary medicine (pediatric and adults), and critical care across the country (Siegel, et al., 2019). It was found that 86% of the 1,604 cases presented at that time had vaped THC (Moritz, et al., 2019). Therefore, these individuals were diagnosed with EVALI (Moritz, et al., 2019).

As cases continued to role in and the death toll rose, the CDC recommended that individuals avoid all THC containing vaping products and to use caution with other vaping products as the causative agent remained unknown (Moritz, 2019). Recommendations for clinicians included asking a detailed social history surrounding vaping of any patient who presented with respiratory symptoms. These questions would include substance vaped (nicotine, cannabis, other substance or unknown), where this substance was obtained, frequency and quantity of vaping (Siegel, et al., 2019). If EVALI was suspected, chest x-ray was the first indicated test. Laboratory tests included a complete blood count (CBC), erythrocyte sedimentation rate (ESR), respiratory viral panel, and urine toxin screen (Siegel, et al., 2019). Chest radiograph of patients with EVALI would show bibasilar infiltrates with ground glass opacities (Viswam, et al., 2019). CBC may be normal or have an increased white blood cell count without eosinophilia (Viswam, et al., 2019).

EVALI is a diagnosis of exclusion ruling out other etiologies related to infectious (viral or bacterial) allergic, or toxic sources. The elimination of differential diagnoses helps to raise suspicion for EVALI. Siegel et al., (2019) stated patients with suspected EVALI should be admitted to the hospital if oxygen saturations are less than 95% on room air, the patient has

symptoms of respiratory distress (tachypnea, increased work of breathing) or has comorbidities of asthma, tuberculosis, cystic fibrosis or chronic obstructive pulmonary disease that will decrease their respiratory reserve (Siegel, et al., 2019). Patients that do not meet these criteria but have suspected EVALI should be treated empirically for community acquired pneumonia with ceftriaxone and azithromycin and followed up within 24-48 hours (Davidson, et al., 2019; Siegel, et al., 2019).

Patients with EVALI who were admitted to the hospital required supplemental oxygen and several required mechanical ventilation due to the severe lung injury (Dicpinigaitis, et al., 2019). Computed tomography scan of the chest confirmed chest radiograph findings of diffuse basilar-predominant infiltrates with ground-glass opacities but also showed tree-in bud infiltrates (Davidson, et al., 2019). Tree-in-bud infiltrates indicate a degree of airway obstruction and this obstruction was confirmed on spirometry testing showing a restrictive ventilatory defect (Viswam, et al., 2018). Patients were treated with methylprednisone for the obstruction and symptoms improved (Davidson, et al., 2019). Several patients had bronchoscopy completed with bronioalveolar lavage that was negative for alveolar hemorrhage but showed lipid-laden macrophages (Dicpinigaitis, et al., 2019). One patient had video-assisted thoracoscopic surgical lung biopsy (VATS biopsy) showing lipid filled macrophages, high levels of cholesterol deposits and inflammation (Viswam, et al., 2018).

Therefore, it was concluded that EVALI symptoms were a result of exogenous lipoid pneumonia (Davidson, et al., 2019). With an identified disease, clinicians still needed to find the cause of the lipoid pneumonia. Why was there a sudden influx of cases when electronic cigarettes had been available for over ten years? The initial thought was there must be a

connection between marijuana and EVALI since almost 90% of EVALI patients had vaped marijuana (Moritz, et al., 2019).

Currently, recreational marijuana is legal in 11 states and medicinal marijuana is legal in 47 states (McNamara, 2020). As rates of legalization increase, so do rates of marijuana being vaped and the age of users is decreasing (Knopf, 2018). No person under the age of 21 should have access to marijuana outside of medical purposes. Research has shown that cannabis use in adolescence leads to decreased brain development, lower educational achievement and inferior psychosocial functioning (Knopf, 2018). Adolescents and children that live in areas with high rates of marijuana dispensaries are twice as likely to vape marijuana and have a younger age of onset than children from other areas (Knopf, 2018).

In addition to the risks associated with vaping marijuana, there are also risks of vaping unregulated products. In states where recreational marijuana is not legal, companies have started to promote CBD as a safer option. CBD and THC are the two main components of marijuana (Poklis, et al., 2018). THC gives users the 'high' sensation and is viewed as more controversial than CBD. CBD has been promoted as a sleep aid, anxiolytic and antidepressant (Poklis, et al., 2018). CBD products are permitted to have up to 0.3% THC. Unfortunately, there is no manufacturing standards to ensure the safety or quality of CBD (Poklis, et al., 2018).

Nine commercially available CBD vaping oils were reviewed and two serious cannabimimetics were identified. The first was 5F-ADB which is a Drug Enforcement Agency (DEA) Schedule 1 drug due to side effects of agitation, psychosis, tachycardia and death. The other substance, dextromethorphan, is found antitussives and has numerous drug-to-drug interactions leading to contraindications. Additionally, there is limited information about the effects of dextromethorphan when inhaled. Dextromethorphan leads to roughly 30 poisonings a

year for adolescents aged 13-18 (Poklis, et al., 2018). This is an extremely dangerous finding as CBD has been marketed as safe and there was no listing of potential contaminants or side effects that could happen from these impurities.

As the number of EVALI cases rose significantly in the summer/fall of 2019, clinicians scrambled to find a cause. Due to the lack of regulation, there were numerous possible causative agents. The first potential culprit that was investigated as the hygroscopic substances used in vaping liquid. Propylene glycol and glycerol are commonly used as humectants in conjunction with flavoring and nicotine, THC or other substances (Chaumont, et al., 2019). Propylene glycol is the main ingredient in many e-cigarette cartridges and can make up 90% of the content (Palazzo, 2013). These substances are labeled "generally safe" when ingested but research is lacking on how these substances affect the body when inhaled. This is an important question since the lung tissue is a moist environment and hygroscopic substances absorb fluids. Researchers hypothesized that propylene glycol and glycerol would lead to dehydration of lung tissues, and alterations in mucocilliary clearing system causing airway obstruction (Chaumont, et al., 2019). These substances are unable to cross biological membranes and foreign substances can trigger proinflammatory cytokines further irritating the airways and leading to airway constriction (Chaumont, et al., 2019).

Unfortunately, nicotine has shown similar inflammatory responses and damages in lungs leading to chronic obstructive pulmonary disease and cancers. With this new method of nicotine (or other substance) delivery, it is important to identify other potentially harmful ingredients. The researchers' goal was to identify if propylene glycol and glycerol had similar or worse effects on lung tissue as nicotine (Chaumont, et al., 2019).

Twenty-five young men (median age 23 years) were recruited to assess the impact of propylene glycol and glycerol on lung function (Chaumont, et al., 2019). The individuals were randomly assigned electronic cigarettes with only propylene glycol and glycerol and electronic cigarettes with these materials and nicotine (Chaumont, et al., 2019). Prior to vaping, 30 minutes after and 150 minutes after, pulmonary function tests (PFTs) as well as blood and urine samples were obtained (Chaumont, et al., 2019). Pulmonary function testing as well as arterial tension testing showed airway constriction and decreased oxygen levels at 30- and 150-minute intervals for both groups (Chaumont, et al., 2019). This shows that nicotine is not the causative agent of respiratory issues in individuals who smoke but in fact the propylene glycol and glycerol were the cause (Chaumont, et al., 2019). It is proposed that these substances were deposited in the epithelium of large airways as well as embedding in the terminal portions of the bronchioles and alveoli (Chaumont, et al., 2019).

Another causative agent that was investigated was metal nanoparticles that were released from the coil heating agent in vape pens. Since there is no combustion in electronic cigarettes or vape pens, a metal coil is used as the heating device (Lerner, et al., 2016). When the pen is turned on, the coil heats up, causing the liquid vape solution containing propylene glycol, glycerol, water, flavoring and nicotine or marijuana to vaporize (Lerner, et al., 2016). Through this process, metal nanoparticles are also released and inhaled by consumers (Lerner, et al., 2016). These nanoparticles, particularly copper nanoparticles, lead to increased mitochondrial stress, DNA damage and oxidative stress (Lerner, et al., 2016). Human lung fibroblasts were exposed to various heavy metals found in vaping pens in an Air-Liquid Interface System culture (Lerner, et al., 2016). Damage was noted as quickly as fifteen minutes after exposure to e-cigarette aerosols containing heavy metal nanoparticles (Lerner, et al., 2016). This finding

validates the notion that vaping is not a safer alternative to combustible cigarettes (Lerner, et al., 2016). Cigarette smoke induces cell death via mitochondria dysfunction leading to apoptosis (Lerner, et al., 2016). E-cigarette aerosols also cause cellular and DNA damage through copper nanoparticle induced oxidative stress (Lerner, et al., 2016). These findings also show that there is a risk to vapers regardless of the type of e-cigarette solution consumed.

A final causative agent that underwent investigation was vitamin E acetate. Vitamin E is used commonly in multivitamins and lotions with minimal complications. Like other substances, there is limited to no data on the impact inhaling vitamin E acetate has on lung tissue (Blount, et al., 2020). Vitamin E acetate is used with THC-containing products to improve aroma and taste as well as lower the cost (Blount, et al., 2020). When EVALI cases were skyrocketing, vaping products were analyzed and nearly 50% of individuals with EVALI had detectable levels of vitamin E acetate in their vaping liquid (Blount, et al., 2020). Without any research to understand the cause of vitamin E acetate on lungs, researchers attempted to identify this substance as the causative agent of EVALI (Blount, et al., 2020).

Researchers obtained bronchoalveolar lavage (BAL) samples from bronchoscopies of 51 patients with presumed EVALI (Blount, et al., 2020). These samples were compared to BAL samples from 99 healthy individuals. Samples were analyzed using isotope dilution mass spectrometry to identify possible toxicants (Blount, et al., 2020). In addition to vitamin E acetate, researchers were looking for DPPC, cannabinoids, plant oils and diluent terpenes, all hypothesized causative agents (Blount, et al., 2020). In the 51 EVALI cases, 48 had detectable levels of vitamin E acetate and no traces of other causes (Blount, et al., 2020). When compared to the healthy individuals, no level of vitamin E acetate was present (Blount, et al., 2020).

While this information was promising in identifying the culprit, researchers did not yet know the mechanism of action for EVALI induced from vitamin E acetate (Blount, et al., 2020). Vitamin E acetate, also known as alpha-tocopheryl acetate, has a long aliphatic tail (Blount, et al., 2020). This tail would allow the molecules to penetrate surfactant leading to changes in surfactant consistency from gel to crystalline (Blount, et al., 2020). When this occurs, surfactant is unable to maintain the surface tension necessary to keep the small airways open (Blount, et al., 2020). Even worse, vitamin E acetate can dissociate at high temperatures with a biproduct of ketene, a known respiratory irritant (Blount, et al., 2020). Both of these factors place Vitamin E Acetate as the likely culprit of EVALI, not nicotine or THC (Blount, et al., 2020).

As mentioned earlier, EVALI was due to exogenous lipoid pneumonia. Though vitamin E acetate, found in THC-containing e-cigarette liquid, is a key player, it is not the only factor that makes e-cigarettes dangerous (Blount, et al., 2020). Propylene glycol and glycerol can cause dehydration and irritation of fragile alveoli leading to a change in surface tension and surfactant functionality (Chaumont, et al., 2019). Copper nanoparticles elicit DNA damage and oxidative stress leading to inflammation and possible long-term changes to lung cell function and structure (Lerner, et al., 2016).

Gaps in the Literature

As mentioned throughout this paper, there are numerous serious gaps in literature. Initial review of the literature revealed few high level research evidence. The majority of current data available being expert opinion or case studies. Electronic cigarettes have been on the market for almost fifteen years, unfortunately there is limited longitudinal studies to guide providers though. Research into the longitudinal effects of vaping needs to be conducted. There is also a need for high quality randomized control trials to prove the severity of adverse effects. Direct RCTs may

be difficult and unlikely due to ethical issues involving adolescents and young adult health, but cohort studies are an alternative. Additionally, research is needed to ascertain how chemicals affect the body when inhaled versus ingested.

Discussion

During the late summer of 2019, an influx of respiratory symptoms in young vapers is partially attributed to the addition of Vitamin E Acetate to THC containing vaping liquids. Vitamin E Acetate improved taste and decreased cost for dealers but induced exogenous lipoid pneumonia in consumers. Vitamin E Acetate penetrates surfactant, changing the surface tension in the lungs leading to lung dysfunction (Blount, et al., 2020). Removing Vitamin E Acetate from vaping liquid is prudent to preventing more EVALI cases. Alas there is limited regulation in regard to manufacturing marijuana-containing vaping liquids due to limited legalization (Poklis, et al., 2019). Adolescents who vape marijuana are at an increased risk for EVALI compared to adolescents who do not vape marijuana.

The aforementioned statements should not be interpreted as deeming vaping nicotine or other products as safe. Other factors that promote lung dysfunction with vaping are the humectants propylene glycol and glycerol. Both components are deemed “safe” for consumption, but this does not translate to mean safe for inhaling the substances. When inhaled, these hygroscopic compounds dehydrate surrounding structures by absorbing adjacent fluid. This change in moisture level effects mucocilliary clearing in the bronchioles causing inflammation and obstruction (Chaumont, et al., 2019).

Combustible cigarette smoke has thousands of carcinogenic products, but electronic cigarette aerosol is not without risk. Consumers are also at risk for adverse effects from vaping due to the metal heating coil. The coil can release heavy metal nanoparticles that are inhaled into

the lungs. These nanoparticles, particularly copper, induce mitochondrial stress, damage cellular DNA and lead to oxidative stress (Lerner, et al., 2016).

In regard to marijuana consumption, it was thought to be inevitable that marijuana and electronic cigarettes would combine. Unfortunately, even though this has happened, there is a significant lack in regulation surrounding marijuana manufacturing. Products like CBD that have been promoted as healthy contain significant impurities. 5F-ADB and dextromorphone lead to serious complications including psychosis or death (Poklis, et al., 2018). Identification of these cannabimimetics is concerning since they are not naturally occurring in marijuana. The lack of regulation surrounding marijuana products must be addressed to protect consumers.

As providers, the goal is to do no harm and educate patients on decisions that will provide them with the highest quality of health. It is difficult for providers to accomplish this goal in regard to electronic cigarettes due to the lack of research, and lack of regulation. When a patient presents attempting to quit combustible smoking, electronic cigarettes have been deemed as effective as other FDA approved smoking cessation tools. But electronic cigarettes have significant risks and too many unknowns to make them a safe alternative to combustible cigarettes. Also, with the identification of vitamin E acetate, propylene glycol and glycerol as potentially harmful agents, providers can suggest patients understand what is in the liquid they are vaping. Reading labels and educating patients on risk factors will be beneficial for patients to protect themselves.

Implications for Future

Recommendations for Clinical Practice

The initial presenting feature for 95% of patients with EVALI was vague respiratory symptoms (Blount et al, 2020). A thorough history in a nonjudgmental way is imperative to

illicit behavioral choices surrounding vaping and substance use. Understanding what substances are vaped, where these substances were obtained, frequency of vaping and duration of vaping are key questions. If EVALI is suspected, initial diagnostics include chest radiograph, CBC, liver transaminases, ESR and urine toxicology. Chest radiograph may show signs of lipoid pneumonia including bibasilar, ground glass opacities and tree-in-bud findings. If patient has history of respiratory illness that will decrease pulmonary reserve, such as asthma, oxygen saturation <95% on room air or signs of respiratory distress, admission to hospital with pulmonary consultation is warranted. If treated outpatient, empirical medications include corticosteroids, antibiotics for community acquired pneumonia (Amoxicillin plus a macrolide) and antivirals as appropriate. Patient should be followed-up in clinic within 24-48 hours and demonstrate proper education on worsening symptoms that would warrant admission (Ramirez, 2019; Siegel, 2019).

Recommendations for Research

EVALI is an evolving health problem and therefore has minimal high-level evidence. It is proposed that decreasing amount of inhaled toxic smoke from combustible cigarettes, which contains tar, ammonia, carbon monoxide and hydrogen cyanide will improve respiratory symptoms, but no research has taken place to support or dispute this hypothesis (Budney, et al., 2015). Other research has begun to understand the negative effects of humectants in the lungs. Research is needed to understand how other biproducts such as Vitamin E, coconut oil**,** effect the body when inhaled. It is also necessary to perform longitudinal studies on individuals to assess systemic effects of electronic cigarette use over time.

Recommendations for Education

Providers and patients need to be educating on the associated risks with vaping and the lack of evidence to support vaping as a healthier alternative to smoking. Education is also needed

surrounding marijuana as this will become more and more common with increasing legalization. Adolescents in high-density dispensary areas are two times more likely to vape marijuana than their counterparts living in other areas (Knopf, 2018). Therefore, education should be prioritized for schools and families in these areas so they are informed of the risk of vaping and the risk of using marijuana at a young age (decreased brain development, lower educational achievement).

There is also education needed for providers in identifying EVALI. While cases have decreased, it is important to identify these cases early as patients can decompensate quickly if not treated appropriately. Providers should ask all patients a thorough social history regarding vaping and educate tobacco users that vaping is not a good option for smoking cessation (Truth Initiative, 2019). Any individual who vapes should be encouraged to quit, especially those vaping marijuana (Moritz, et al., 2019). Additionally, symptomatic patients should obtain a chest radiograph which may show bibasilar infiltrates. EVALI is a diagnosis of exclusion so empirical treatment of possible community acquired pneumonia is indicated. If admitted, high dose methylprednisone was shown to decrease airway inflammation and improve respiratory symptoms (Dicpinigaitis, et al., 2019).

Recommendations for Policy

There is a need for more regulation surrounding cannabis production. Currently, people are using cannabis concentrates that are higher in potency than marketed due to lack of regulation (Budney, et al., 2015). Without regulation, there is no means for consumers to know the ingredients of the product they are consuming leading to large variations in purity and potency. This variability is quite dangerous as increased consumption of highly potent cannabinoids have been linked to psychotic episodes. Therefore, as legalization of marijuana

continues to grow, it is imperative that there are policies in place to regulate the potency and purity of cannabinoid concentrates (Budney, et al., 2015).

Another policy consideration is the density of dispensaries. Adolescents that live in an area with high numbers of dispensaries in a small area (therefore high density) have a two-time higher likelihood of vaping marijuana and are more likely to start at a younger age. This is concerning since chronic cannabis use in adolescence is associated with inhibited brain development leading to lower educational achievement and psychosocial functioning (Knopf, 2018). There is also a positive association between length of legalization and likelihood of vaping in that the longer a state has legalized marijuana, the adolescent is more likely to have vaped (Knopf, 2018). This is important information for legislators to remember as legalizing recreational marijuana is gaining traction. Limiting the number of dispensaries or not allowing dispensaries within certain areas of schools may help deter adolescents from trying marijuana.

Additionally, regulation regarding electronic cigarette usage in smoke-free zones is needed. Years of work and legalization may be undermined with electronic cigarettes being used in schools and other public places. Due to their discrete design, it is difficult to identify vape pens. Also, there is no research on any second-hand effects of those inhaling the vapor or flavorings inadvertently.

Conclusion

The spike in EVALI from August 2019 to December 2019 can be partially attributed to Vitamin E Acetate. This substance has the same consistency of THC oil, so it is used to cut THC oil and increase profits for distributors. Vitamin E Acetate is not used in e cigarettes containing nicotine (Blount, et al., 2020). Therefore, those individuals who used THC containing e-cigarettes were at an increased risk for EVALI compared to those who did not consume THC.

This does not mean that there are no side effects associated with vaping nicotine or other marijuana products. Vaping products that contain propylene glycol and glycerol are at risk for increased lung injury and inflammation due to changes in surfactant and gas exchange (Chaumont, et al, 2019).

Due to lack of regulation surrounding marijuana containing vape solution, consumers are at an increased risk for complications. Without regulation, purity and potency levels are not guaranteed. Additionally, as recreational marijuana becomes legalized in more states, adolescents are at an increased chance of vaping at a younger age if they live in an area with high dispensary density (Knopf, 2018). Providers need to stay abreast on these topics to ensure they are educating patients appropriately and identifying any complications associated with vaping.

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Appendix

Table 1

Database Search Description

Database	**Restrictions Added to Search**	**Dates Included in Database**	**General Subjects Covered by Database**
CINAHL Plus	Full Text, peer reviewed	2015-2019	Nursing e-books and journals covering all aspects of nursing and other medical professions
MEDLINE (PubMed)	Full text, peer reviewed	2015-2019	Citations, abstracts and full text articles for health professionals in the health care system
Cochrane	Apply related words, search within text	2015-2019	Bibliography of controlled trials
Academic Search Premier	Full Text, peer reviewed	2015-2019	Over 4,600 publications covering all areas of interest
Nursing and allied Health Database	Full Text, peer reviewed, Adolescent (13-18)	2015-2019	All aspects of nursing and affiliated healthcare

Table 2

Data Extraction Process

Date of Search	**Key Words**	**CINAHL**	**MEDLINE (PubMed)**	**Cochrane**	**Academic Search Premier**	**Nursing and allied Health Database**
10/10/19	Vaping Cannabis	35(**9)**	81	2(**1)**	87 (**10)**	69 (**7)**
10/10/19	'Vaping cannabis' AND 'lung injury'	2(**2)**	7(**3)**	0	4 (**2)**	16 (**2)**
10/10/19	'Vaping cannabis' AND 'lung injury' AND 'adolescents	**0**	1 (**1)**	**0**	11 (**1)**	9 (**1)**
10/22/19	'Vaping or e-cigarettes' AND	569	5 (**5)**	77 (**4)**	317	317

Date of Search	Key Words	CINAHL	MEDLINE (PubMed)	Cochrane	Academic Search Premier	Nursing and allied Health Database
	lung injury' AND 'adolescent'					
10/25/19	'vaping' AND 'lung disease'	11	35 (**5**)	5 (**2**)	34 (**4**)	109
10/25/19	'vaping' AND 'teens' AND 'lung disease'	1 (**1**)	15 (**3**)	0	3 (**0**)	18 (**3**)
11/12/19	'cannabidiol' AND 'e-cigarette	3 (**2**)	6 (0)	0	6(**1**)	15 (**3**)

BOLD: articles reviewed for match with systematic review inclusion criteria.

- Some of the bold articles are seen in multiple databases leading to skewed numbers
- Searches yielding more than 100 results were refined prior to evaluating articles

Table 3

Characteristics of Articles Included and Excluded

Reference	Included or Excluded	Rationale
Ahmad, S.., Zafar, I., Mariappan, N., Husain, M., Wei, C.-C., Vetal, N., . . . Ahmad, A. (2019). Acute pulmonary effects of aerosolized nicotine. *American Journal of physiology*, L94-L104.	Excluded	Focus on nicotine MULTIPLE DATABASES
Atkins, G. (2015). Acute inhalational lung injury related to the use of electronic nicotine delivery system. *Chest Infections*, 83A.	Excluded	Focus on nicotine
Blount, B. C., Karwowski, M. P., Shields, P. G., Morel-Espinosa, M.,	Included	Vitamin E Acetate link to EVALI

Reference	Included or Excluded	Rationale
Valentin-Blasini, L., Gardner, M., . . . Cowan, E. (2020). Vitamin E acetate in bronchoalveolar-lavage fluid associated with EVALI. *The New England Journal of Medicine*, 697-705.		
Budney, A. J., Sargent, J. D., & Lee, D. C. (2015). Vaping cannabis (marijuana): parallel concerns to e-cigs? Society for the study of addiction, 1699-1704.	Included	Impact of vaping cannabis MULTIPLE DATABASES
Chaumont, M., van de Borne, P., Bernard, A., Van Muylem, A., Deprez, G., Ullmo, J., . . . Debbas, N. (2019). Fourth generation e-cigarette vaping induces transient lung inflammation and gas exchange disturbances: Results from two randomized clinical trials. *American Journal of Physiology*, L705-L719.	Included	Vaping, regardless of marijuana, leads to impaired arterial oxygen tension MULTIPLE DATABASES
Davidson, K., Brancato, A., Heetderks, P., Mansour, W., Matheis, E., Nario, M., . . . Fox, D. (2019). Outbreak of electronic-cigarette-associated acute lipoid	Included	Pathophysiology behind EVALI

Reference	Included or Excluded	Rationale
pneumonia-North Carolina, July-August 2019. *Morbidity and Mortality Weekly Report*.		
Davies, M. J., Birkett, J. W., Kotwa, M., Tomlinson, L., & Woldetinsae, R. (2017). The impact of cigarette/e-cigarette vapour on simulated pulmonary surfactant monolayers under physiologically relevant conditions. *Surface and interface analysis*, 654-665.	Excluded	Cigarettes versus e-cigarettes
Dicpinigaitis, P. V., Trachuk, P., Fakier, F., Teka, M., & Suhrland, M. J. (2019). Vaping-associated acute respiratory failure due to acute lipoid pneumonia. *Lung*, 1-4.	Included	Increased evidence supporting link between cannabis vaping and lipoid pneumonia
Ewing, S. W., Lovejoy, T. I., & Choo, E. K. (2017). How has legal recreational cannabis affected adolescents in your state? A window of opportunity. *American Journal of Public Health*, 246-247.	Excluded	Opinion piece, not focused on vaping marijuana but instead marijuana use in any form (edibles, etc.)
He, T., Oks, M., Esposito, M., Steniberg, H., & Makaryus, M. (2017). 'Tree-in-bloom': Severe acute lung	Excluded	Single case-study. Middle-aged male. MULTIPLE DATABASES

Reference	Included or Excluded	Rationale
injury induced by vaping cannabis oil. *Annals of the American Thoracic Society*, 468-470.		
Knopf, A. (2018). Teen cannabis vaping and edibles increased in cannabis states. *Alcoholism & drug abuse weekly*, 5-7.	Included	Legalizing marijuana and increased number of dispensaries increases vaping use MULTIPLE DATABASES
Lerner, C. A., Rutagarama, P., Ahmad, T., Sundar, I. K., Elder, A., & Rahman, I. (2016). Electronic cigarette aerosols and copper nanoparticles induce mitochondrial stress and promote DNA fragmentation in lung fibroblasts. *Biochemical and biophysical research communities*, 620-625.	Included	Vaporized oxidants lead to mitochondrial stress
Miech, R., Johnston, L., O'Malley, P. M., Bachman, J. G., & Patrick, M. E. (2019). Trends in adolescent vaping, 2017-2019. *New England Journal of Medicine*.	Excluded	Nicotine vaping rates only
Moritz, E. D., Zapata, L. B., Kekiachvili, A., Glidden, E., Annor, F. B., Werner, A. K., . . . Pet. (2019). Update: Characteristics of patients in a national	Included	Midwest Outbreak, Patient characteristics

Reference	Included or Excluded	Rationale
outbreak of e-cigarette, or vaping, product use-associated lung injuries-United States, October 2019. *MMWR: Morbidity & Mortality Weekly Report*, 985-989.		
Palazzolo, D. L. (2013). Electronic cigarettes and vaping: A new challenge in clinical medicine and public health. A literature review. *National Library of Medicine*, 1-20.	Included	Literature review from 2008-2013 e-cigarette use
Poklis, J. L., Mulder, H. A., & Peace, M. R. (2018). The unexpected identification of the cannabimimetic, 5F-ADB, and dextromethorphan in commercially available cannabidiol e-liquids. *Forensic Science International*, e25-e27.	Included	Unregulated marijuana products can lead to increased risk
Siegel, D. A., Jatloui, T. C., Koumans, E. H., Kiernan, E. A., Layer, M., Cates, J. E., . . . Mitchk. (2019). Update: Interim guidance for health care providers evaluating and caring for patients with suspected e-cigarette, or vaping, product use	Included	Midwest Outbreak, clinician guidelines MULTIPLE DATABASES

Reference	Included or Excluded	Rationale
associated lung injury- United States, October 2019. *MMWR: Morbidity and Mortality Weekly Report*, 919-927.		
Viswam, D., Trotter, S., Burge, S. P., & Walters, G. I. (2018). Respiratory failure caused by lipoid pneumonia from vaping e-cigarettes. *BMJ Case Reports*, 1-4.	Included	Case study that discusses glycol as culprit to lipoid PNA not marijuana/THC or nicotine
Windle, S. B., Wade, K., Filion, K. B., Kimmelman, J., Thombs, B. D., & Eisenberg, M. J. (2019). Potential harms from legalization of recreational cannabis use in Canada. *Canadian Journal of Public Health*, 222-226.	Excluded	Information specific to Canada (indigenous people, regulations etc.)

Shaded rows indicate included articles

Table 4

Literature Review Table of All Studies Included

Citation	Study Purpose	Pop(N)/ Sample Size (n)	Study Design/Level of Evidence	Variables / Instruments	Intervention	Findings	Implications
Blount (2020)	Diagnostic proof of Vitamin E linkage	51 patients with confirm	Level III: case-cohort study	Assess BAL washings	91 healthy BAL	Vitamin E was the only	Vitamin E as one of the causes of EVALI

Citation	Study Purpose	Pop(N)/ Sample Size (n)	Study Design/Level of Evidence	Variables / Instruments	Intervention	Findings	Implications
	to EVALI	ed EVALI			washings	contaminant present	
Budney, Sargent & Lee (2015)	Prompt awareness for the need for increased scientific research into marijuana vaping		Level IV: Case Series	Vaping cannabis or cannabinoids, e-cigarette use		Lack of quality research regarding vaping marijuana	Need for increased scientific research on the long-term effects of cannabis vaping
Chaumont et al (2019)	Assess effects of e-cigarettes on inflammation, gas tension and PFTs	25 young tobacco users	Level II	Vaping	Vape with or without nicotine	Vaping induced airway epithelial injury	Glycerol and propylene glycol, not nicotine or THC may be the cause of EVALI
Davidson, et al (2019)	Pathophysiology of EVALI	5 North Carolina Patients with history of vaping cannabis	Level VII			Lipoid pneumonia in all 5 patients	Possible pathophysiology behind EVALI
Dicpinigaitis (2019)	Add information to evolving understanding of EVALI	28-year old male	Level V			Acute lipoid pneumonia due to vaping cannabis	Increased support for cannabis induced lung disease
Knopf (2018)	Assess the effect	2,630 cannabis	Level VI	Facebook survey		Increased	As legalizati

Citation	Study Purpose	Pop(N)/ Sample Size (n)	Study Design/Level of Evidence	Variables / Instruments	Intervention	Findings	Implications
	of marijuana legalization on how it is consumed	-using youth age 14-18				length of legalization and increased number of dispensaries correlates with increased vaping of THC	on of marijuana continues, vaping THC products will become an increasing burden
Lerner et al. (2016)	Determine mechanism of lung injury from vaping		Level III/ case control	DNA fragmentation assay, ELISA, 2-tailed t-test	Exposure of e-cigarette aerosols to lung cells	E-cigarette aerosols cause inflammatory changes	E-cigarettes with nicotine may have deleterious long-term effects Copper nanoparticles
Moritz, et al (2019)	Describe patient characteristics and vaped substances as well as EVALI-associated deaths	1,604 cases of EVALI with 34 deaths	Level VII: expert opinion	Review of EVALI cases reported to CDC	n/a	86% of patient with EVALI used THC-containing products within	Encourage patients to avoid vaping THC-containing products

Citation	Study Purpose	Pop(N)/ Sample Size (n)	Study Design/Level of Evidence	Variables / Instruments	Intervention	Findings	Implications
						the previous 3 months	
Palazzolo, (2013)	Literature Review	73 research articles	Level V/ Literature Review			Need for more RCT and scientific research to guide practice	More research is needed, unclear guidelines for providers (benefit versus harm)
Poklis, Mulder & Peace (2018)	Cannabidiols contain surprising contaminants	9 CBD infused liquids	Level IV	Analyze liquids via DART/MS and GC/MS		5F-ADB and dextromethorphan found in cannabidiol products	Unregulated distribution of these products increases consumers risk of injury
Siegel, et al (2019)	Provide practice guidelines for practitioners regarding EVALI	339 EVALI medical records submitted to CDC	Level VII: expert opinion	Review of EVALI cases reported to CDC	n/a	Pertinent history, vitals, respiratory viral panel, CBC, toxicology, CXR and	Interim guidance for practitioners

Citation	Study Purpose	Pop(N)/ Sample Size (n)	Study Design/Level of Evidence	Variables / Instruments	Intervention	Findings	Implications
						CT chest	
Viswam et al (2018)	Evaluate lipoid pneumonia associated with e-cigarettes	1 case report	Level VII			Glycol leads to lipoid pneumonia not other additives	No difference in risk between THC and nicotine

EVALI: electronic-cigarette (e-cigarette), or vaping, product use-associated lung injury
RB-ILD: respiratory bronchiolitis interstitial lung disease
DART/MS: Direct Analysis in real time mass spectrometry
GC/MS: Gas chromatography mass spectrometry