MEDICAL COLLEGE OF WISCONSIN SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Brief Summary of Vaping and E-cigarette Associated Lung Injury

by Thomas Ringsred, 2021 PharmD Candidate, Isabelle Sviatoslavsky, 2021 PharmD Candidate

Electronic nicotine delivery systems (ENDS) include e-cigarettes, vape pens, e-hookah devices, e-pipes, and vaporizers which are the infamous devices implicated in the recent "vaping crisis". "Vaping" has become a media-frenzied buzzword, but what is really known about these products? In the last few years the use of these products has skyrocketed, especially among teens. According to the Food and Drug Administration (FDA), e-cigarette use among high school students increased 78% from 2017 to 2018 and 48% among middle school students.[1] The current widespread use of ENDS is especially concerning due to a recent outbreak of vaping related illness termed E-cigarette or Vaping Associated Lung Injury (EVALI).[2]

Cases of EVALI were first reported to the Centers for Disease Control and Prevention (CDC) in August of 2019. As of January 7th 2020, among the 50 states, District of Columbia (D.C.), Puerto Rico and the U.S. Virgin Islands there have been 2,602 reported cases including 57 deaths.[2] To be qualified as an EVALI case by the CDC, patients must have no identifiable infectious, cardiac, rheumatologic, or neoplastic cause of their disease, and must have used an e-cigarette or vape device in the prior 90 days.[3]

Symptoms of EVALI can develop over days to weeks and are not limited to the pulmonary system. Patients may present with respiratory (shortness of breath, cough, chest pain), gastrointestinal (nausea, vomiting, diarrhea), and constitutional (fever, headache) symptoms.[4] Some reports suggest up to 94% of patients have required hospitalization. Intensive care needs are common; mechanical ventilation has been reported as high as 32% in some case series and invasive therapies such as lung transplant and extra corporeal membrane oxygenation have been required.[5] The disease has primarily affected those who are younger (median age 24, range 13-78) and male (67%).[6] No single product has been tied to EVALI, and patients report varied e-cigarette or vaping patterns. Use of a tetrahydrocannabinol (THC) containing product has been reported by 80% of EVALI patients, while 13% report exclusively nicotine, 1% report exclusively cannabidiol (CBD), and 5% report neither nicotine, CBD nor THC. While vaping-related lung illness has been reported in patients using nicotine, THC, and CBD, no specific causative agent has been identified.[6]

Media excitement and lack of definitive explanations behind these phenomena have generated public uncertainty and patients may have questions surrounding these products. It is important for pharmacists and other healthcare professionals to be familiar with vaping and understand the use and misuse of such products. This article summarizes evidence-based literature regarding the harmful effects of vaping, highlights under investigated areas that require further research, and outlines the role healthcare providers can play in proper use and patient safety.

Possible Causative Agents

The FDA is currently testing samples from a variety of different vaping devices for "priority toxicants" including plant oils, diluent terpenes, medium-chain triglycerides, coconut oil, petroleum distillates, and vitamin E acetate. At this time, there is no distinct substance that has been universally identified among these patient samples.[2]

Vitamin E acetate has been identified by the CDC in bronchoalveolar lavage fluid analyses from EVALI patients. Vitamin E acetate is an additive found in some THC-containing e-cigarettes and vaping products, where it is often used as a thickening agent. The CDC tested 51 EVALI patient samples from 16 states and found vitamin E acetate in 48/51 samples. Additionally, they evaluated 99 samples from smokers, e-cigarette users, and non-smokers and found no vitamin E acetate present.[7] These findings suggest that vitamin E acetate may be linked to EVALI as a chemical of concern for individuals using e-cigarette or vaping products. When vitamin E acetate is taken orally as a supplement or used topically on the skin, it does not usually cause harm. Per the CDC, past studies suggest it may harm normal lung functioning when inhaled.[2] It has been theorized that vitamin E acetate may interfere with surfactant functioning, or that acetate may be released during vaporization as a toxic irritant known as a ketene. Though the theories surrounding toxicity have not been explicitly tested, the CDC is attempting to quantify ketene levels in EVALI patient lungs. While evidence supports an association of vitamin E acetate with EVALI, it is not known if it is correlation or causation, and other possible causes may still be identified.[7]

Other ingredients of concern include the plethora of additives in THC vaping products. The majority of the samples procured by the FDA or characterized by EVALI patients contain THC and the vaping products used were often obtained from informal sources such as friends or online dealers.[8] While use of THC-containing vaping products may correlate to lung injury, more investigation needs to be done to assess the relationship between EVALI and other concerning additives - sweeteners, flavoring agents, cooling concentrates, nicotine salts, and herbal blends.[3] Diacetyl is a flavoring agent that

has previously been used to add a butter-like taste to foods such as microwave popcorn. According to the Occupational Safety and Health Administration (OSHA), diacetyl has been linked to severe lung disease and obliterative bronchiolitis in microwave popcorn factory workers after they were exposed to the flavoring agent.[10] Diacetyl has been identified in vaping e-liquids, and even in products that claimed to have no diacetyl on their packaging.[11]

Several studies have reported that potentially toxic short-chain aldehydes such as formaldehyde, acetaldehyde, or acrolein can be produced as a result of the heating coil, which can reach temperatures exceeding 350°C, chemically changing components of the e-liquid.[12,13] The concentrations of these byproducts vary depending on wattage. Acrolein for example did not form until a wattage of at least 20W. One study by Geiss and colleagues (2016) found a steep increase in carbonyl production when applying a battery output of at least 15W which generated temperatures between 200-250°C with the product in their study.[12] However, their "experienced vaper" responded poorly to 20W as it caused a negative sensorial experience (intolerable heat, flavor, density) suggesting most users would not likely apply such a wattage.[12]

Other concerns include the presence of heavy metals such as tin, cobalt, lead, nickel, or cadmium which originate from the cartomizer and end up in the aerosolized product. Lead and cadmium have been identified in these aerosolized products and are known to cause respiratory distress as well as disease. These were tentative results and further evaluation is necessary to assess the significance of these metal concentrations due to the difficulty of measuring trace levels of metals.[14] As is, both the FDA and CDC continue to analyze patient-provided samples and emphasize that no universal causative agent has been identified.[3]

Suggestions for Healthcare Professionals

Management of EVALI is focused on ruling out other causes and providing symptomatic supportive therapies. Due to the rapid progression of injury, early recognition is crucial for disease management. If a patient presents with respiratory, gastrointestinal, or constitutional symptoms a detailed history of vape or e-cigarette product use should be performed. Ideally, healthcare providers should try to classify the substances in question (THC, cannabis, nicotine, modified products); product source, product brand and name; duration and frequency of use to help identify the source of the issue. To confirm EVALI diagnosis, other causes must be ruled out. Completion of a respiratory virus panel is strongly recommended for patients presenting with generalized EVALI symptoms, especially during influenza season. Additional testing to rule out community-acquired pneumonia, as well as possible radiographic lung imaging should also be considered. The ambiguity of its presentation paired with the lack of specific biological markers make recognizing EVALI difficult; therefore, diagnosis is primarily exclusion-based.

Further, due to the rapid progression of injury, early recognition is crucial for disease management. Pointed verification measures may include history of vape use, respiratory or gastrointestinal symptoms, oxygen saturation, infectious disease status, and a chest x-ray.[3]

Inpatient admission should be strongly considered in patients with EVALI, especially when accentuated with overt respiratory distress, comorbidities that compromise pulmonary reserve, or an O_2 saturation of less than 95%. A typical intervention to be considered is the use of a short course of corticosteroids, a mainstay treatment for respiratory exacerbations. Use of corticosteroids may worsen certain infections so it may be beneficial to avoid starting them until other causes have been ruled out. Early prophylactic treatment for community-acquired pneumonia or influenza should be considered until ruled out. Respiratory supportive therapies including oxygen, inhaled bronchodilators and antimuscarinics, and more invasive therapies such as intubation may be required. Due to the high severity of disease burden, multidisciplinary care is appropriate. Specialists should be involved at multiple points in care such as medical toxicology, pulmonology, psychiatry, addiction medicine, infectious disease, and rheumatology.[3,15]

After the patient has been stable for 24-48 hours the patient may be considered for discharge. If discharged, a follow-up visit should be made ideally within 48 hours. Follow-up should include pulse-oximetry with consideration for a repeat chest radiograph, spirometry assessment, and diffusion capacity testing. Further follow-up with a pulmonologist within 2-4 weeks and 1-2 months later is recommended.[3,15]

Outpatient management is individualized and often mirrors inpatient interventions, such as the empiric use of antimicrobials or antivirals and potential use of corticosteroids. Follow-up is again recommended within 24-48 hours to further assess potential progression of lung injury. Outpatients should have normal oxygen saturation (omitting the need for inpatient admission), but should have access to appropriate care, a social support system, and be instructed to seek medical care if respiratory symptoms worsen.[3,15]

Re-exposure to products could lead to recurrence of disease. Providers should strongly advise the patient to discontinue use of vaping products, as well as provide education and resources to interventions such as addiction counseling or FDA approved nicotine replacement therapies.[3,15] It's important to note that some suggestive data has led to the belief that ENDS may help in quitting cigarette smoking. The U.S. Preventive Services Task Force, an assembly of health experts specialized in recommendations for preventive health care, concluded that current evidence is insufficient to make this claim.[16] Lastly, all patients should be screened for and provided appropriate vaccinations, including influenza and pneumococcal.[3,15]

New Legislation

On December 20th, 2019 the President signed legislation to raise the federal sale age for all tobacco products, including cigarettes and e-cigarettes from 18 to 21 years.[17,18] Prior to this federal law, 16 states had already raised the minimum sale age of tobacco products. The hope is this new law will help save lives by reducing tobacco use. Tobacco and nicotine users who are 18 or 19 years often supply younger classmates with these products. By raising the sale age to 21 years, an age most students will reach after completing high school, the number of students using these products at younger ages will hopefully be reduced. Additionally, the increase in legal age may minimize the extent cigarette, cigar, and e-cigarette companies target young users.[18] While this new law may reduce the use of vaping products among teens, it has the potential to incite students to look for alternative sources of obtaining these products. This could result in an increased use of products obtained from informal sources which, as previously mentioned, potentiates the risk for consumption of unknown substances that may induce EVALI.

Conclusion

The outbreak of EVALI is concerning, especially due to the primarily younger patients it affects, and the current rise of vaping use amongst the youth. Many questions remain regarding what the cause of this outbreak is, and what the future regulation of these products will be. There are many agents that could be to blame, but currently there have not been any definitive findings. An association with EVALI has been found with vitamin E acetate containing THC products, but not every case has been linked to these ingredients. More evidence is critical to isolating the primary offenders. With the current state of the outbreak, no product is known to be safe, and avoidance of e-cigarette or vaping products is the only way to ensure avoidance of disease.[2]

Diagnosis is primarily focused on ruling out other possible causes and verifying a history of vaporizer usage. Recommended treatment tends to be patient specific and involves respiratory distress control interventions as well as supportive care. The CDC is currently providing up-to-date guidance on their website www.cdc.gov and encourages clinicians to report possible cases of EVALI to local or state health deparments.[2,19] The CDC has promised to continue to track cases, communicate actionable recommendations, and to establish standard lab procedures to assist with public health investigation and patient care.[2]

Thomas Ringsred and Isabelle Sviatoslavsky are Doctor of Pharmacy Candidates at the Medical College of Wisconsin School of Pharmacy in Milwaukee, WI.

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