E-cigarette or vaping product use-associated lung injury (EVALI): a cautionary tale

Tetrahydrocannabinol-containing (THC) products with vitamin E additives are implicated in the pathogenesis of EVALI

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Electronic cigarettes, or e-cigarettes, are battery-powered devices that heat liquids containing nicotine and other chemicals in order to produce vapour.[1] "Vaping" is the act of inhaling the vapour produced by an e-cigarette.[1] First marketed in 2005, e-cigarette use is viewed by many as less harmful than traditional cigarette smoking, and championed as a strategy for smoking cessation.[1–3] A detailed discussion of e-cigarette use in smoking cessation is available in the United States Surgeon General's 2020 report, and is beyond the scope of this article; however, the report states that "there is presently inadequate evidence to conclude that e-cigarettes, in general, increase smoking cessation".[2] Thus far, no e-cigarette product for the therapeutic purpose of smoking cessation has been submitted to Australia's Therapeutic Goods Administration for safety evaluation or approval.

Vaping in the US was initially associated with nicotine-containing solutions. However, it is important to note that nicotine or nicotine salts may no longer be the only active ingredient in vaping solutions.[1,4,5] In particular, unregulated vaping solutions or "home-brew" products that contain tetrahydrocannabinol (THC) oil, or cannabinoids, can be obtained in the US.[4,6]

Vaping solutions come in a wide range of flavours, many designed to appeal to adolescents.[1,2] Indeed, e-cigarette manufacturers have used celebrity endorsements and social media-based marketing campaigns to target adolescents, and these strategies appear to have been highly successful.[1,2] There has been significant uptake of vaping among tobacco-naive high school students, particularly in the US, where it is estimated that one in four high school students are current e-cigarette users;[7] moreover, in 2019, 14% of year 12 students reported vaping cannabis in the preceding 30 days.[8]

Between 2011 and 2018, e-cigarette use increased among US high school students from 1.5% to 20.8%, even when traditional cigarette use declined from 15.8% to 8.1%.[9] Consequently, from 2017 to 2018, overall use of tobacco products (traditional and e-cigarettes combined) increased from 19.6% to 27.1%.[9] In contrast, e-cigarettes use among adults in the US has remained largely stable at 8.1 million e-cigarette users (3.2%).[10] It is possible that for young non-smokers, e-cigarettes may normalise smoking and serve as a gateway to nicotine dependency and traditional cigarette smoking, although this is strongly debated.[1,9]

In 2016, the Australian National Drug Strategy Household Survey reported that e-cigarette use within the 12–17 and 18–29 years age brackets was about 7.1% and 16% respectively.[11–13] The 2017 Australian

secondary students' alcohol and drug survey found that 13% of students had used an e-cigarette at least once.[14] Of the 2410 students who used an e-cigarette, 48% reported that they had never smoked a traditional tobacco cigarette before using an e-cigarette.[14] E-cigarettes may be perceived by young people as "a cool new gadget" and "safer than smoking".[1]

Unfortunately, it has become abundantly clear that the use of illicitly sourced e-cigarettes can be dangerous.[10] In 2019, disturbing reports emerged of an acute and, for some, deadly outcome from vaping.[15] Across the US, e-cigarette users began to be admitted to hospitals with acute respiratory failure. In August 2019, the first fatality was documented in Illinois, while 200 other cases across 22 states were under investigation by the Centers for Disease Control and Prevention (CDC).[15] This epidemic has spread very rapidly. There have been over 2800 hospitalised cases reported from every US state and territory and a total of 68 deaths.[16] Patients were predominantly male (66%) and under 35 years of age (76%).[6] [Correction added on 2 July 2020 after first online publication: Information has been updated on the second last sentence.]

The CDC has termed this new disease "e-cigarette or vaping product use-associated lung injury" (EVALI)[17] and has proposed four obligatory criteria for its diagnosis:

- use of an e-cigarette ("vaping") in the 90 days before symptom onset;[18]
- pulmonary infiltrates or ground glass opacities on x-ray or computed tomography scan;
- absence of pulmonary infection (defined by negative respiratory viral panel, negative influenza polymerase chain reaction, negative urinary pneumococcal antigen and sputum culture including *Legionella*, and bronchoalveolar lavage [BAL] culture); and

- no evidence of an alternative plausible diagnosis such as a cardiac disease or a neoplastic process.[17,18]

Patients with EVALI typically present with both respiratory (dyspnoea, cough, fever) and gastrointestinal (nausea, vomiting, diarrhoea, abdominal pain) symptoms.[15,19] Usually, there is no prior history of respiratory disease. Diagnosis may be challenging, as EVALI can mimic infective pneumonia and gastrointestinal symptoms may sometimes precede respiratory symptoms.[15] Respiratory failure may be severe enough to require invasive ventilation and intensive care support.[15,19]

Imaging findings include ground glass opacities on chest imaging,[20] suggesting diffuse lung injury with bronchiolitis obliterans and cryptogenic organising pneumonia.[19] Pathologically, limited lung biopsies have shown acute lung injury, acute fibrinous pneumonitis and diffuse alveolar damage.[21] "Foamy" or lipid-laden macrophages are often seen, suggestive of lipoid pneumonia.[15]

Aetiology and pathophysiology of EVALI: reasons for its recent emergence

Careful epidemiological investigation has revealed two key findings explaining the recent emergence of EVALI after more than a decade of e-cigarette use. Firstly, 80% of hospitalised patients with EVALI have admitted to using THC vaping products.[6] Eighty-four per cent of the reported THC products were acquired via informal channels and were probably manufactured outside of regulated facilities.[15] The CDC identified "Dank Vapes" — a group of largely counterfeit THC-containing products — as the most commonly reported THC brand across the US and used by 56% of patients with EVALI admitted to hospital.[6] In contrast, only 13% of hospitalised patients with EVALI reported exclusive use of nicotine-containing products; however, traces of THC were found in BAL samples.[6,19] There may be unreliable self-reporting and it is possible that the nicotine e-cigarettes may have been contaminated by black-market THC additives. Most patients reported using combination products containing either THC, cannabidiol or nicotine.[6]

Secondly, there is mounting evidence that a specific additive to vaping solutions — vitamin E acetate — played a major role in the 2019 EVALI outbreak.[19,20] It is hypothesised that vaping the vitamin E acetate oil causes direct lung injury and lipoid pneumonia.[21] Supporting this, BAL fluid from 51 patients from 16 states diagnosed with EVALI yielded vitamin E acetate in 94% (48/51) of the BAL samples.[19] In an analysis of the THC-containing e-cigarette products used by 12 patients, vitamin E acetate was found in products from 11 patients.[19] It is likely that this substance was added as a diluent or filler, and this practice appears to be a very recent development.[19] The same chemical analysis performed on THC e-cigarette products seized in 2018 did not find vitamin E acetate.[19]

Current evidence shows that THC-containing products with vitamin E acetate additives are implicated in the pathogenesis of EVALI.[21] Given the outbreak has only manifested in the past 18 months, it is likely that the addition of these substances into e-cigarette solutions is a very recent occurrence.

The CDC outlines three broad tenets for treating suspected EVALI:

- cover possible infective agents with empiric broad-spectrum antibiotics;
- administer systemic steroids (optimal dose unknown); and
- provide best supportive care with oxygen therapy and close monitoring.[15,17,20]

In mild to moderate cases, the decision to start steroids can be delayed until culture results exclude or identify potential infectious pathogens.[17] In severe cases, systemic corticosteroids should be given early due to the potential life-threatening nature of EVALI.[20] There have been reports of progressive ventilatory failure despite administration of high dose steroids (methylprednisolone 1 mg/kg), with patients requiring extracorporeal membrane oxygenation.[20]

So far, there are no confirmed reports of EVALI in Australia. Unlike in the US, nicotine-containing liquids are illegal in Australia and can only be obtained on medical prescription for personal use.[11] The sale of e-cigarettes to people aged under 18 years is also illegal.[11] In practice, however, a 2015 survey of Australian e-cigarette use found that 90% of users purchased e-cigarettes and liquids from unregulated online stores.[11] Even legal nicotine-free liquids sold in Australia have been found to contain traces of nicotine and other toxic substances, with no regulation of products.[22] Most Australian e-cigarette users are therefore vulnerable to the possibility of potentially dangerous substances being added to solutions, as has occurred in the US.

Conclusion

Vaping THC oil contaminated with vitamin E acetate is linked with severe lung injury and death. With more than 2800 cases of EVALI reported and 68 deaths, e-cigarettes are definitely not risk-free. Australian clinicians should maintain vigilance and ask every patient about e-cigarette use. Adults using nicotine-containing e-cigarettes as an alternative to cigarette smoking should not revert to tobacco smoking.[2] A reasonable and precautionary strategy is to advise patients that little is known about the long term effects of e-cigarettes, and also to inform users that severe lung disease and death have occurred mainly with unregulated solutions. We recommend further research and ongoing field monitoring of e-cigarette usage patterns in Australia.

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