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REVIEW

Cannabis and electronic cigarette use in youths

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ABSTRACT

Marijuana use has grown following legalization of use for medical and recreational purposes in many countries, particularly in youths. The prevalence of regular marijuana product use among American high school seniors now exceeds tobacco smoking. Electronic cigarettes are increasingly used to aerosolize cannabinoids, mostly delta-9-tetrahydrocannabinol, which are inhaled into the lungs and systemically absorbed. They have frequently been marketed to adolescents, applying many of the same arguments used to promote nicotine-containing products, and their perceived safety led to earlier and more frequent use. They have other attractions to youths, since they are easy to use, easy to obtain, and easily concealed from others. However, the emergence of electronic cigarette or vaping product use-associated lung injury (EVALI) highlighted the risks associated with some of these products. Because many of cannabinoid-containing products are illegally produced and sold, there is little regulation or quality control. With the rise of cannabinoid vaping, pediatric pulmonologists will need to be familiar with the clinical effects of these products and their potential adverse effects.

IMPACT STATEMENT: Cannabis use is growing among adolescents, and as seen during the EVALI epidemic, vaping cannabinoid-containing solutions can cause significant lung injury, largely from toxic solvents and other additives. Pediatricians and respirologists need to be aware of the potential risks of these products in their patients.

KEY WORDS
Marijuana; cannabinoid; tetrahydrocannabinol; electronic cigarettes.

INTRODUCTION

With the legalization and decriminalization of marijuana, its use has rapidly grown in many countries. In the United States, almost 43% of young adults between the ages of 19 and 30 years reported using marijuana in the past year (1), and cannabis and its derivatives have gained popularity among youths (1-6). More than 40% of American high school seniors report some marijuana use, and the prevalence of regular cannabis product use among students now exceeds tobacco smoking. Increasingly, electronic nicotine delivery systems, which termed electronic cigarettes in this paper, are used to aerosolize cannabis products, which are inhaled into the lungs and systemically absorbed (7, 8). The perceived safety of cannabis has led to the belief that vaping cannabinoids could be a useful harm reduction strategy. However, the surge of acute lung injury in adolescents and young adults has highlighted the risks of some of these products, and dramatically showed that cannabinoid vaping can cause pulmonary morbidity and mortality in youths

(9). As this phenomenon grows, pediatric pulmonologists and other providers will need to understand the potential adverse effects in teenagers.

In this short review, we will describe the use of cannabis-based products and rise of vaping among adolescents, their clinical and pharmacological effects, and the potential hazards that have emerged.

MARIJUANA USE IN YOUTHS

Derived from the *Cannabis sativa* plant, cannabis products include dried leaves, oil extracts, and concentrates that contain numerous toxicants, including terpenes, flavonoids, alkaloids, and cannabinoids, such as cannabinol, cannabidiol (CBD), delta-8-tetrahydrocannabinol (THC), and delta-9-THC (**Figure 1**), which have variable psychoactive effects (4).

Inhaled cannabis has a rapid onset of action, and active agents their effect through the endocannabinoid system, which consists of endocannabinoids, endogenous lipid-based retrograde neurotransmitters, and cannabinoid receptors that are expressed in the brain (10, 11). There are two major cannabinoid receptors. CB1 receptors are found in the central nervous system, preganglionic sympathetic neurons, smooth muscle, and myocardial cells, while the CB2 receptor is predominantly expressed in peripheral smooth muscle, myocardium, and vascular endothelium (11). delta-9-THC is an agonist for both CB1 and CB2 receptors, binding inhibits neurotransmission leading to impairments in learning, memory, attention, and tachycardia (12), and has reported analgesic and anti-inflammatory effects (13). CB1 and CB2 are expressed in human lungs, found on resident alveolar and monocyte-derived macrophages (14, 15), and cannabinoids have been shown to alter the pulmonary immune response (14, 16, 17).

The greatest concern with cannabis is misuse and addiction (4). Chronic cannabis use can lead to addiction with earlier age at initiation increasing the risk for addiction, since preclinical studies have shown that the developing central nervous system is more vulnerable to the adverse long-term effects. Roughly 20% of people who began using marijuana as teenagers become addicted (18).

Inhaled phytocannabinoids can dilate the airways through CB1 receptors binding on postganglionic vagal nerves, which decreases bronchomotor tone by inhibiting acetylcholine release (10). However, regular marijuana smokers frequently have chronic bronchitis symptoms, characterized by persistent cough, sputum production, and wheezing (19-27). Late effects of marijuana smoking include airway inflammation and obstruction, and bronchoalveolar lavage fluid collected from young adults had neutrophilic inflammation, similar to tobacco smokers with elevated markers of oxidative stress and necrotic cell death. Endobronchial biopsies have revealed epithelial damage with goblet cell hyperplasia and squamous metaplasia (1, 21, 28, 29).

Chest imaging studies of marijuana smokers are often interpreted as normal but can show lung hyperinflation with parenchymal or emphysematous changes. Spontaneous pneumothorax or pneumomediastinum has

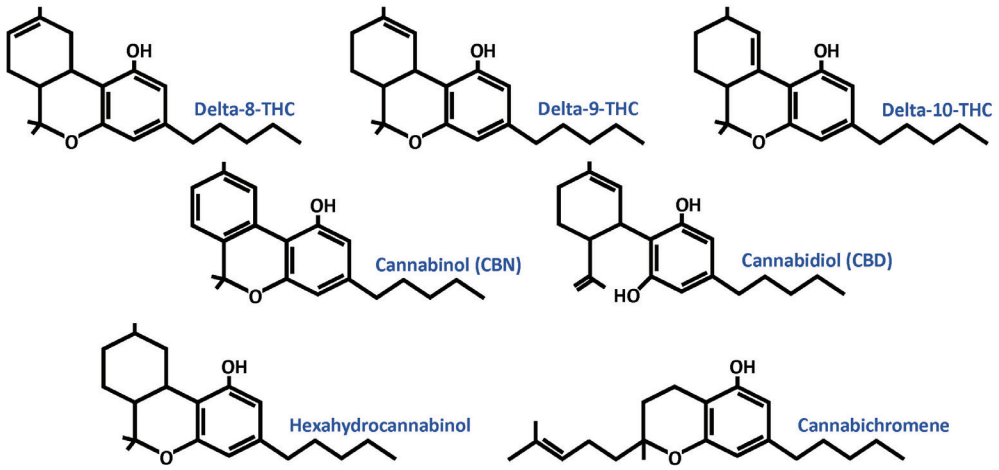

Figure 1. *Schematic diagram showing structural similarities of cannabinoids found in cannabis.*

been linked to marijuana use, likely related to repeated deep inhalations and breath-holds (28). The impact of marijuana smoking on pulmonary function varies between studies. A higher proportion of young adult, regular marijuana users had airway obstruction compared to nonsmokers (24), but other investigators failed to find a relationship between marijuana use and pulmonary function measures (30).

ELECTRONIC CIGARETTES AND CANNABINOID VAPING

For decades, smokers have sought "safer" products, and like nicotine-containing products, electronic cigarettes can be used to aerosolize cannabis concentrates or liquid cannabinoids (31). Teenagers use electronic cigarettes to inhale both nicotine and cannabis. In fact, these devices have been used to deliver cannabis-related products for more than a decade. Electronic cigarettes come in many different shapes and sizes, but generally have a similar design, using a heating element or atomizer to create an aerosol from a solution of flavorants, propylene glycol, glycerin, and other additives and chemicals (32).

Electronic cigarettes use has grown worldwide, and now the dominant tobacco product used by teenagers (33). American adolescents who use electronic cigarettes, over half of high school students reported current use of cannabinoid products (33). Approximately one-in-five senior high school students reported cannabinoid vaping (34, 35). Similarly, Canadian surveys showed that electronic cigarette use in high-school students steadily increased to 15%, and vaping was the most common way cannabis was used (2, 36). The Global Youth Tobacco Survey showed that electronic cigarette use among Italian adolescents increased from 0% in 2010 to 17.5% in 2018 (37), but he percentage of Italian youths who use electronic cigarettes to vape cannabinoids is unknown since it is illegal. Nevertheless, these products can still be found (38) in many countries, available through internet venders.

The most common active ingredient is delta-9-THC in cannabis electronic cigarettes, but other naturally occurring and novel synthetic cannabinoids are appearing on the market, such as delta-10-THC, cannabichromene, and hexahydrocannabinol (38) (**Table 1**). Various chemicals and solvents used in their extraction are also found in these products, particularly those found on the black market, including medium-chain triglyceride oils, phytols and triethyl citrate (38). The amount of delta-9-THC and other chemicals delivered with each puff varies and depends on vaping solution and power of the device.

More potent cannabis concentrates are increasingly available for electronic cigarettes, which increases the psychoactive effects of the product and likelihood of withdrawal when cannabis is discontinued. "Dabbing" is another method teenagers use to inhale cannabinoids, during which cannabis concentrates, called dabs, are vaporized on a heated surface connected to a water pipe (38-40). Roughly 4% of American high school students use dabbing, and the purity and potency of cannabis concentrates in many products is largely unknown (40).

Many of the same arguments used to promote electronic cigarettes over combustible tobacco cigarettes have been applied to vaping cannabis (7, 41-43). Electronic cigarettes were frequently marketed to adolescents with claims of lower risk compared to combustible products, and perceptions of relative safety led to earlier and more frequent use, as well as decreased motivation to quit or reduce use (6, 44). These products have other attractions to youths, since they are disposable, easy to use, easy to obtain, and easily concealed from others (2, 32, 33).

Like nicotine-containing solutions, fruit and candy flavored cannabinoid products are popular among adolescents and contributed to early, electronic cigarette initiation (45). As seen with other electronic cigarettes, cool "vaping culture" have emerged in schools that has promoted cannabinoid vaping among peers (46). Social influences, underestimation of risk, greater access to cannabinoid products, psychobehavioral co-morbidities, and other substance abuse can also contribute to their continued use (38, 47).

Constituents of vaping solutions can be harmful when inhaled. Analyses of the electronic cigarette cartridges showed products contained detectable levels of known carcinogens and toxic chemicals to which users could be exposed. Some delta-8-THC containing products have been shown to be contaminated by chemicals that are toxic to the lung, including sulfuric acid, hydrochloric acid, trifluoroacetic acid or *p*-toluenesulfonic

acid (**Table 1**) (48). High temperature can cause vegetable glycerin and propylene glycol to their degrade, producing formaldehyde, acetaldehyde, acrolein, and propionaldehyde, chemicals known to injure the lungs. Like nicotine-containing products, cannabinoid-containing vape solutions can be contaminated by impurities, like various solvents. Hot coils and wicks can release metallic particles into aerosol (49), and flavoring chemicals can also be toxic to the lung. Several analyses have shown that quality control of cannabinoid-containing products can be inconsistent or non-existent (38), and several US states have recalled hundreds of different products because they contained harmful additives.

Epidemiologic studies have found increased rates of bronchitis, emphysema, and asthma in adolescent and young adult electronic cigarette users (27). Use of cannabinoid-containing electronic cigarettes has been associated with wheeze or shortness of breath in young adults, often described as bronchitis, even after adjusting for use of nicotine-containing products (50). Delta-9-THC has not been shown to be toxic, but propylene glycol and glycerin aerosols can induce inflammatory cytokine release and reduced epithelial cell viability, worsened by the addition of some flavorants

ACUTE LUNG INJURY ASSOCIATED WITH VAPING

Individual cases of severe respiratory diseases linked to electronic cigarette use have been reported in young adults and teenagers for over decade (51). Four years ago, clusters of acute lung injury were linked to electronic cigarette use (9, 52). Termed “electronic cigarette or vaping product use-associated lung injury” (EVALI) by the US Centers for Disease Control, it was defined as the onset of pulmonary infiltrates on chest imaging that occur within 90 days of electronic cigarette use, without an alternative etiology. EVALI was described mostly in adolescents and young adults, with 35% of the affected 20 years or younger, often using products obtained illegally. Nearly all patients presented with respiratory symptoms, such as cough, chest pain, and shortness of breath, but also had gastrointestinal and constitutional symptoms, like abdominal pain, vomiting, diarrhea, fever, and weight loss (52, 53). In the United States, 2,807 individuals required hospital admission and 68 individuals died due to EVALI, and most patients were treated with systemic corticosteroids (53). These products were often obtained from friends or family, with 80% of patients reported using delta-9-THC (9), often purchased illegally (53, 54).

EVALI is a syndrome and laboratory findings are frequently nonspecific (51). Chest imaging often shows lower lobe disease with diffuse ground-glass opacities, alveolar consolidations, and occasionally centrilobular nodules (**Figure 2A**) (54-56). The histopathology of

Table 1. *Various chemical constituents previously found in cannabis electron cigarette aerosols (38).*

Cannabinoids
delta-9-tetrahydrocannabinol
delta-8-tetrahydrocannabinol
delta-10-tetrahydrocannabinol
cannabidiol
hexahydrocannabinol
cannabichromene
Solvents and cutting agents
propylene glycol
glycerol
vitamin E acetate
medium-chain triglycerides
phytol
Flavorants
terpenes
ß-myrcene
d-limonene
linalool
ß-caryophyllene
cinnamaldehyde
ß-caryophyllene
diacetyl
vannilin
menthol
Trace chemicals and contaminants
benzene
xylene
isoprene
sulfuric acid
trifluoroacetic acid
p-toluenesulfuric acid
heavy metals (e.g., cobalt)
endotoxins

EVALI varies. Many of the features were consistent with airway-centered chemical pneumonitis (51, 54-56), likely related to exposure to aerosolized toxins (57). Lung biopsies often revealed an organizing pneumonia (**Figure 2B**), but before EVALI, respiratory bronchiolitis, interstitial lung disease, lipoid pneumonia, eosinophilic pneumonia, and diffuse alveolar hemorrhage were described (58-64). “Foamy” macrophages are a nearly universal finding (56), suggesting toxic injury, and changes involve the more distal airways, primarily bronchioles. Neutrophilic inflammation is also found and sometimes confused for an acute infection.

Various chemicals were found in analyses cartridges collected from individuals who suffered EVALI, including polycyclic aromatic hydrocarbons, nitrosamines, endotoxins, diacetyl, squalene, and squalene. Heating certain constituents of vape solutions can yield noxious thermal degradation product. Often found in vaping solutions, terpenes like ß-myrcene can break down into potentially hazardous volatile organic chemicals. (38) Much of the work has focused on a vitamin E acetate, a lipophilic, synthetic form of vitamin E, since many (but not all) of these cartridges had high levels of this cutting agent used to dilute the cannabis oil (65-67). Vitamin E acetate potentially displaces endogenous surfactant, and when heated can degrade to ketene, a toxin that acetylates proteins and damages alveolar capillaries (68). The direct effects of the cannabinoid on the lung without vitamin E acetate are unclear. While vitamin E acetate has since been banned from use, it may continue to be used in illicit products.

Little research has been conducted examining the health effects of these cannabinoid-containing products, even in countries where these products are legal (51). In murine models, delta-9-THC-containing aerosols can induce inflammatory cytokines expression (14, 16, 38). Bronchoalveolar lavage fluid from mice treated with cannabinoid-containing electronic cigarettes had increased concentrations of neutrophils and CD4-positive lymphocytes. They can downregulate nitric oxide production, suppress chemotaxis, and impair phagocytic activity in murine macrophages (69, 70). Lung homogenates from mice treated with cannabinoid-containing electronic cigarette aerosols had lower concentrations of surfactant-associated proteins, and oxidized phosphatidylcholines could potentially disrupt surfactant function (16, 38). Cannabinoid-containing vaping solutions stimulated production of reactive oxygen species from bronchial epithelial cells and disrupts the epithelial barrier. Mucociliary clearance was also impaired, with greater susceptibility to infections described in aerosol-exposed laboratory animals (38).

CONCLUSIONS

Cannabis use is growing and often considered an innocuous, recreational activity among youths. However, its safety has not been fully established. As seen in the EVALI epidemic, inhaling an aerosol containing cannabinoids and other unknown constituents has risks, even to healthy adolescents.

Recently, the American Thoracic Society published a workshop report that reviewed the EVALI epidem-

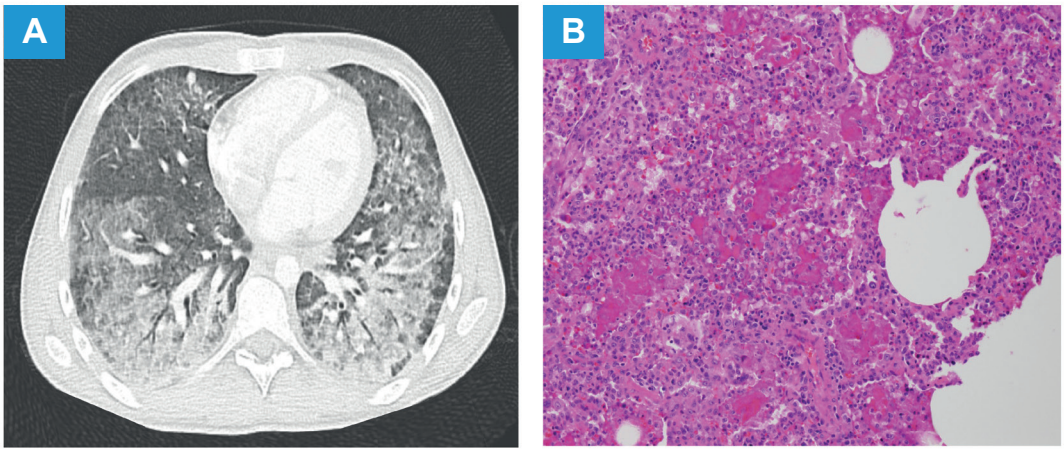

Figure 2. (A) *Computed xray tomography of the chest obtained from a young man hospitalized with EVALI, which revealed alveolar infiltrates, ground glass opacities, and centrolobular nodules;* ***(B)*** *histopathological changes in lungs of the same patient showing multifocal organizing pneumonia.*

ic (51), and its authors advocated for more research to better understand the risks of electronic cigarettes. The toxicities of cannabis-derived products have been understudied, and research has been slowed by regulatory restrictions since marijuana and its constituents are considered a controlled substance. Such data are needed to establish safety of these products and determine whether more systematic regulation of cannabis-based products is needed, ensuring consistent manufacturing standards, and reducing their risks (51). Until then, pediatricians need to be aware that cannabinoid vaping is more common than most think, understand its potential hazards, and considered this possibility when presented with an adolescent with unexplained, acute or chronic respiratory symptoms. Indeed, acute lung injury associated with electronic cigarettes did not begin with EVALI, nor has it ended.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of interests

The Author has declared no conflict of interests.

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Authorship

Professor Thomas W. Ferkol is the only Author of the manuscript.

Author contributions

TWF conceived the work, reviewed available literature, and wrote the review. He approved the publication of the content and agreed to be accountable for all aspects of the work.

Ethical approval

Human studies and subjects

N/A.

Animal studies

N/A.

Publication ethics

Plagiarism

This is a review article and all original studies are cited as appropriate.

Data falsification and fabrication

All the data correspond to the real.

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