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REVIEW

Cannabis and Lung Health: Does the Bad Outweigh the Good?

Alan G. Kaplan

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ABSTRACT

Cannabis use is growing, with multiple medical 'indications' and approval for recreational use in many countries. This article will review some of the respiratory complications to cannabis use, which include lung function changes, lung destruction, increased risk of lung and head and neck cancer, and others. These are mostly related to smoking, and the co-administration of nicotine makes the risks a bit difficult to measure. However, with many reports of EVALI, electronic vaping-associated lung injury, being related to cannabis coadministration, it appears that the safest administration of cannabis, as far as lung health, is orally.

Keywords: Lung function; Cannabis; THC; CBD; Asthma; COPD; Lung cancer; Pneumothorax; Respiratory

Key Summary Points

Evidence collection for cannabis effect on the lung is complicated by issues of accurately understanding the dose given, the concomitant use of nicotine making the effect of the cannabis difficult to assess, and the evidence mostly including only THC while CBD is getting more common to be used for medicinal purposes.

Smoking THC is associated with worsening respiratory symptoms of cough or sputum, wheezing, and shortness of breath, increased incidence of acute bronchitic episodes or clinic visits for acute respiratory illness.

Cannabis leads to hyperinflation and increased large airway resistance, with little evidence of airflow obstruction (cf. nicotine smoking, which causes airflow obstruction).

The association of smoking cannabis to lung cancer risk is not clear.

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A. G. Kaplan (✉)
Family Physician Airways Group of Canada, Respiratory Effectiveness Group, Primary Care Respiratory Research, OPRI, local LHIN Pulmonary Rehabilitation Clinics, University of Toronto, 7335 Yonge Street, Thornhill, Toronto, ON L3T 2B2, Canada
e-mail: for4kids@gmail.com

Multiple case reports show a relationship of cannabis smoking to multiple respiratory conditions including cannabis-induced complications including aspergillosis, hemoptysis, emphysema and secondary pneumothorax, hypersensitivity pneumonitis, eosinophilic pneumonitis, ARDS, vanishing lung syndrome, and emphysema.

DIGITAL FEATURES

This article is published with digital features, including a video abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.16622608.

INTRODUCTION

Cannabis use is growing, according to the United Nations, with 158.8 million people around the world using marijuana—more than 3.8% of the planet's population. Interestingly, their 2019 stats suggest that globally between 4 and 9.1% of children aged 15–16 years old around the world use cannabis [1]. In 2018, 14% of Canadians aged 15 years or older reported cannabis use in the past 3 months, with 40% of these individuals reporting daily use [2]. Over 94 million people in the US have admitted using it at least once [3]. In December 2020, the United Nations voted to remove cannabis for medicinal purposes from a category of the world's most dangerous drugs [4]. Many countries have legalized its use, leading to the attitude that if it is legal, it must be safe. The myriad of benefits claimed to be had by medical cannabis make it an intriguing choice for physicians and patients. These include potential benefits [5] including chronic pain, especially neuropathic pain [6], spasticity associated with multiple sclerosis, nausea, posttraumatic stress disorder, cancer, epilepsy, cachexia, glaucoma, HIV/AIDS, and degenerative neurological conditions, chemotherapy-induced nausea and vomiting, anorexia and weight loss associated with HIV, irritable bowel syndrome, epilepsy, spasticity, Tourette syndrome, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, dystonia, dementia, traumatic brain injury, addiction, anxiety, depression, sleep disorders, posttraumatic stress disorder, and schizophrenia and other psychoses. The business side of this is staggering, with 2020 estimates that the cannabis industry was worth $16.1 billion in the United States and $19.6 billion worldwide. Positive impacts from the national legalization of recreational cannabis use in Canada beyond recreational use and relief of medical issues include increased tax revenue for the Canadian economy, decreased black market activity, and reduced criminal charges (which disproportionately affect marginalized populations).

METHODS

In 2018, the Canadian Thoracic Society (CTS) formed a group to create a guideline paper on cannabis and respiratory health. Unfortunately, due to the pandemic, this has been delayed. A search of papers was done, and articles were prepared for six PICO questions and reviewed by the panel. I used these papers which were vigorously searched and reviewed as the basis of my evidence and separately searched for any unanswered questions. PICO [7] stands for Population/Intervention/Compare/Outcome. I was subsequently requested to publish on this topic, which I felt would be useful and appropriate as the CTS process had been so delayed and the topic is of such controversy. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

There are many non-respiratory risks of cannabis use [8]. In short-term use, these include impaired short-term memory, impaired motor coordination, risk of injury, e.g., driving, altered judgement, e.g., sexual behaviors leading to risk of STDs, paranoia, and psychosis (usually in higher doses).

In long-term or heavy use, reported issues include addiction (risk is 9% overall, but 17%

for those who start use in adolescence, and up to 50% in those who are daily users), altered brain development, poor educational completion/outcomes, cognitive impairment (IQ levels impaired with frequent use during adolescence), diminished long-term life satisfaction, increased risk of psychotic disorders such as schizophrenia.

As such, legalization in countries such as Canada needs to take this into account, especially in its use in vulnerable groups, such as children and youth, pregnant women, individuals with mental illness, individuals with low socio-economic status, and indigenous populations [9].

In Canada [10], data show that smoking (79%) was the most common method of cannabis consumption reported by people who used cannabis over the previous 12 months, a decrease from 2019 (84%). Other methods of consumption were: eating it in food (52%), an increase from 2019 (46%), vaporizing using a vape pen or e-cigarette (24%), a decrease from 2019 (27%), and vaporizing using a vaporizer (12%), a decrease from 2019 (15%). Onset of action is much quicker when taken by the inhaled route, making it the preferred route for many patients, especially when used recreationally. That being said, for conditions like pain, PTSD, and epilepsy, the oral slower onset but longer duration in products like oils are a realistic alternative. I will deal with studies of inhaled cannabis only, with the preponderance being smoked, but will also discuss vaporization and other methods of smoking like using a waterpipe.

This review is to be based on the respiratory effects of cannabis use. Risks are confounded by the co-administration of nicotine in smoking, often making it hard to separate the actual risk of the cannabis from the tobacco.

DIFFICULTY IN ANALYSIS OF STUDIES

Because of the frequent co-administration of tobacco in people who smoke cannabis, it is difficult to separate the effects of each substance. Smoking tobacco is already recognized to cause symptoms of cough, sputum, chronic bronchitis, wheezing, and shortness of breath. Tobacco smoking leads to airway inflammation and damage to small and large airways causing COPD and to the alveoli causing emphysema. Spirometric measures lead to a progressive loss of lung function as measured by forced expiratory volume in 1 s (FEV1) and FEV1 divided by forced vital capacity (FVC) – FEV1/FVC ratio. Pulmonary function testing shows air-trapping within the lungs, measured with total lung capacity (TLC) or residual volume (RV) or the ratio RV/TLC) as seen on chest X-ray (CXR).

Studies are also limited due to the difficulties in measuring the amount of cannabis used. As a rule, one joint-year is defined as 365 joints smoked. Both the size of a joint and dosing frequency are not reproducible and often self-reported, making reproducibility difficult. Self-reported joint-years to quantify use may be inaccurate, owing to the legality of cannabis use, recall bias, and alteration of behavior by its observation [11, 12].

Cannabis can be smoked in many different ways, which will also alter the net dose effect. As an example, using a water bong will potentially decrease the concentration of inhaled carcinogenic compounds [13]. Using a vaporizer to inhale cannabis rather than combusting it in smoke may reduce pulmonary complications, but the recent epidemic of EVALI [14] is of significant concern for more acute lung complications [15].

Cannabis and tobacco tend to be smoked differently. Typically, cannabis is smoked without a filter, to a shorter butt length, and the smoke is at a higher temperature. Furthermore, cannabis smokers (cf. tobacco alone) take larger puffs, inhale more deeply, hold their breath for longer (about four times longer), and perform a Valsalva maneuver at maximal breath-hold [16]; this leads to differing lung exposure and deposition of components as well as creating the potential for barotrauma [17, 18].

Cannabis is not one drug. There are multiple components including THC (delta-9-tetrahydrocannabinol), CBD (cannabidiol), and terpenes all in differing combinations in different preparations. Most studies have been done with THC and are older. CBD treatment decreased

the inflammatory and remodeling processes in the mouse model of allergic asthma [19]. Newer formulations of THC are of a much higher concentration due to the demand for rapid effect. As such, the conclusions from the THC studies may not be referable to current available strains.

Cannabis smoking via combustion, even without cigarette smoking [20], has been associated with respiratory symptoms, chronic bronchitis, changes in lung function testing, risk of developing COPD, worsening of asthma and COPD, bullous disease, and lung and head and neck cancer due to exposure to carcinogens [21], cardiovascular complications, allergy, and respiratory infections [22, 23]. These elevated risks are presumed to be reduced in methods of consumption that do not include combustion (e.g., vaping, edibles); however, the relative safety of these methods is as yet unknown. I will break down some of the risks in the upcoming sections.

LUNG FUNCTION

Acute Effects of Smoked Cannabis

Cannabis had been used as an asthma treatment since the 19th century [24], with subsequent proof of some bronchodilator effects. Comparatively, smoking a single tobacco cigarette causes acute bronchoconstriction, which has been attributed to an irritant effect of the smoke leading to cholinergically mediated reflex bronchospasm [25]. In contrast, smoking a single "joint" of marijuana (2% THC) created acute bronchodilation in healthy subjects [26], and in patients with mild asthma, with a rapid onset and duration of at least 2 h [27]. This effect, which persisted for at least 1 h, was due to the THC content of the "joint" because the effect was not seen when the THC was extracted but was subsequently reproduced after the "joint" was spiked with synthetic THC [28, 29]. Other studies did not show any bronchodilator effect [30]. Overall, while there may be some bronchodilator effects, they are likely negated by the paradoxical bronchospasm that also occurs with inhalation of combusted materials [31].

Chronic Use of Smoked Cannabis Effects

Old data suggested a possible bronchodilator effect with acute THC use. This has been confirmed [32], but is less than salbutamol, and is lost over time with the effects of combustion when smoked.

In a structured review of cannabis on lung function [23], there was variability in the findings in cannabis-only smokers from a reduction in the FEV1/FVC ratio to no change reported. In a population-based cohort in Dunedin, New Zealand, in a study of 1937 patients, there was no association between chronic marijuana use and change in FEV1 or FEV1/FVC at age 32 but there was an increased FVC [33]. In a cross-sectional study of 7716 US adults from the National Health And Nutrition Examination Study cohort, Kempker [34] showed no effect on FEV1/FVC up to 20 joint-years, but in those with greater than 20 joint-years there was a 2.1-fold risk for FEV1/FVC ratio $< 70\%$, accounted for by a significant increase in FVC and no significant reduction in FEV1. These results suggests that while the FEV1/FVC decreases by $\sim 1.5\%$ in most chronic users, this may not relate to a reduction in FEV1 but to an increase in FVC. These findings represent a major difference in the effects of cannabis compared to the effects of tobacco smoking [23]. It may be quite different in those smoking both cigarettes and cannabis but no additive adverse effects of marijuana on lung function (cf. symptoms) when smoked along with tobacco have been reported [22].

Studies of the pathophysiology of cannabis smoke have shown related large airway epithelial damage, edema, erythema, and increased secretions with goblet cell hyperplasia, loss of ciliated epithelium, and squamous metaplasia on biopsy. There is additive bronchial epithelial damage in combined cannabis and tobacco smokers [35].

In summary, there are different and distinct patterns of lung changes [33] between cannabis and tobacco smokers, indicating different physiologic consequences for the lungs. Cannabis leads to hyperinflation and increased large airway resistance, with little evidence of airflow obstruction or impairment of gas

transfer, whereas tobacco was associated with airflow obstruction, gas trapping, and lower transfer factors.

RESPIRATORY SYMPTOMS

Patients with chronic cannabis smoking show an increased prevalence of chronic cough or sputum, wheezing and shortness of breath, increased incidence of acute bronchitic episodes, or clinic visits for acute respiratory illness. Knowing that tobacco smoking causes these as well, there have been studies done to compare to cannabis-only smokers. In a study from Los Angeles [36], daily cannabis smokers were compared to tobacco-only smokers, combined smokers, and non-smokers. In the smokers of marijuana alone, tobacco alone, or marijuana plus tobacco, the prevalence of chronic cough (18–24%), sputum production (20–26%), wheezing for at least 3 weeks/year (25–37%), and at least two prolonged episodes of acute bronchitis during the previous 3 years (10–14%) were significantly higher than in the non-smokers. However, there did not seem to be any additive effect, as there were no differences between the three active comparator groups of smokers of any kind. In a similar study in Tucson Arizona [37], chronic cough was less common in marijuana-only smokers than tobacco smokers, but the effects of combined smoking of marijuana and tobacco on cough and sputum appeared to be additive. In a 2-year follow-up study from Kaiser Permanente of 452 daily marijuana-only smokers and 450 non-smokers, there was a significant increase in outpatient visits for respiratory illnesses among the marijuana smokers (RR, 1.19; 95% CI 1.01–1.41) [38]. In a Dunedin New Zealand cohort, they corrected for tobacco use and found that early morning sputum production, wheezing apart from colds, nocturnal awakenings with chest tightness, and exercise-induced shortness of breath were increased among the cannabis-dependent subjects by 144% (P = 0.01), 61, 65, and 72%, respectively, compared with non-smokers [39]. In another New Zealand study of adult residents of Wellington, New Zealand [40], the odds ratios (95% CI) for the association of cough with marijuana smoking and tobacco smoking were 1.5 (1.1–1.7) and 1.9 (1.4–2.6), respectively, and of chronic sputum production were 2.0 (1.4–2.7) and 1.6 (1.2–2.2), respectively. There was no evidence of any additive effects of marijuana and tobacco, consistent with the findings in the Los Angeles study. In a survey of older adults (> 40 years) residing in Vancouver, Canada, as part of the Burden of Obstructive Lung Diseases (BOLD) study [41], the odds ratio (OR) for chronic respiratory symptoms was not increased among the 49% of respondents who reported ever using marijuana alone and importantly the concurrent use of marijuana and tobacco was associated with a higher OR for respiratory symptoms (OR, 2.59; 95% CI 1.58–3.62) compared to smoking tobacco alone. Cannabis in addition to tobacco contributed to a diagnosis of COPD at an earlier age with a trend to poorer lung function [42].

As such, there is a lot of conflicting evidence, which highlights the difficulties in these studies, with difficulties in measuring the amount of cannabis actually used due to self reporting of smoking frequency and cannabis dose. That being said, there seems to be a significant association of marijuana use with symptoms of chronic bronchitis that may be comparable to or less than that of tobacco smoking alone. Similarly, evidence is mixed regarding the possibility of additive or synergistic effects of combined smoking of marijuana and tobacco on chronic respiratory symptoms. Looking at this from the point of cessation of cannabis smoking in cannabis-only smokers, there is an improvement of pre-existing respiratory symptoms of chronic bronchitis [43] with symptoms in the quitters being reduced to levels similar to those in never-users [44].

LUNG CANCER RISK

There is obvious concern for cannabis smoking to increase lung cancer risk, as tobacco smoking is the major cause of lung cancer [45], and marijuana and tobacco smoke both contain many of the potent carcinogens [46]. In addition, as marijuana smoking is usually associated

with deeper inhalation, longer breath-holding times, use of unfiltered marijuana cigarettes (''joints'') with a potential for greater delivery of tar to the lungs [47], and the marijuana smoke being even more cytotoxic and mutagenic [48, 49] in comparison with tobacco smoking. Bronchial biopsies have demonstrated that marijuana users show not only manifest airway inflammation but also histopathological and/or molecular changes indicative of precancerous bronchial activity [50, 51]. Endobronchial biopsies from habitual marijuana-only smokers reveal widespread histopathologic alterations that are recognized as precursors to the subsequent development of malignancy [52], such as squamous cell metaplasia and cellular atypia, comparable to those observed in biopsies from tobacco-only smokers [53].

Despite this, epidemiological studies have not always found a definite association. Case-controlled studies and cohort studies have not shown an increased risk [54, 55], while other epidemiological studies have reported associations with lung cancer with heavier marijuana use. For example, a 40-year longitudinal cohort study in 49,321 Swedish conscripts found that those who smoked cannabis > 50 times had a twofold risk of developing lung cancer [56].

Despite the obvious biologic plausibility, the lack of consistent epidemiological evidence might be due to methodological issues including lack of cohort follow-up time into older adulthood (when lung cancer usually becomes clinically manifest), small sample sizes, selection and recall biases, and lack of adjustment for tobacco use in the statistical modeling. However, biologic plausibility can go both ways. There have been anti-tumor effects of cannabinoids in animal [57] and cell culture [58, 59] models.

Multiple case-controlled [60, 61] or cohort [62, 63] studies have shown no evidence of either lung or upper-airway cancer increase [64], especially after being controlled for tobacco use. An early case–control study in New Zealand [65] of marijuana use and lung cancer risk that included only 79 cancer-case subjects and 324 matched control subjects was published in 2008. It only showed that an increased risk was noted among the 14 case subjects and four control subjects in the highest tertile of marijuana use (RR, 5.7; 95% CI 1.5–21.6), corresponding to a life-time history of more than 10.5 joint-years (number of joints per day times number of years smoked, but the numbers were quite small of this group).

In a New Zealand registry trial [66] looking at the risk of head and neck cancers, an increased risk of cancer was found with increasing tobacco use, alcohol consumption, and decreased income, but not increasing cannabis use. The highest tertile of cannabis use (> 8.3 joint-years) was associated with a non-significant increased risk of cancer (relative risk = 1.6, 95% confidence interval, 0.5–5.2) after adjustment for confounding variables. The authors concluded that cannabis use did not increase the risk of head and neck cancers.

Consecutive patients with a newly diagnosed head and neck cancer were prospectively enrolled between 2011 and 2015 in a tertiary center in Hamilton, Ontario [67]. Cannabis users and controls were compared using standard modes of comparison. No significant differences between cannabis users and controls were observed except that cannabis users were more likely to develop primary oropharyngeal cancer ($p = 0.0046$). Two of 59 (3.4%) cannabis users developed a second primary cancer, in comparison to 23 of 454 (5.1%) non-cannabis users. As such, cannabis use (different than tobacco) did not seem to induce an increase in a second primary head and neck cancers.

A study done in Northern Africa [68] looking at 636 cases of nasopharyngeal carcinoma found a higher risk of nasopharyngeal carcinoma with cannabis smokers adjusted for tobacco in those with ever-cannabis smoking and those with lifetime high-dose cannabis smoking (OR, 2.62; 95% CI 1.00–6.86). It did not, however, include cannabis-only smokers, which could limit its relevance.

Studies have also looked at non-respiratory cancers, with no definitive answers but some possible relationships. In a US study following cannabis smokers for a mean of 8.6 years, the findings showed that among non-smokers of tobacco cigarettes, ever having used marijuana was associated with increased risk of prostate cancer (RR = 3.1, CI 1.0–9.5) and nearly

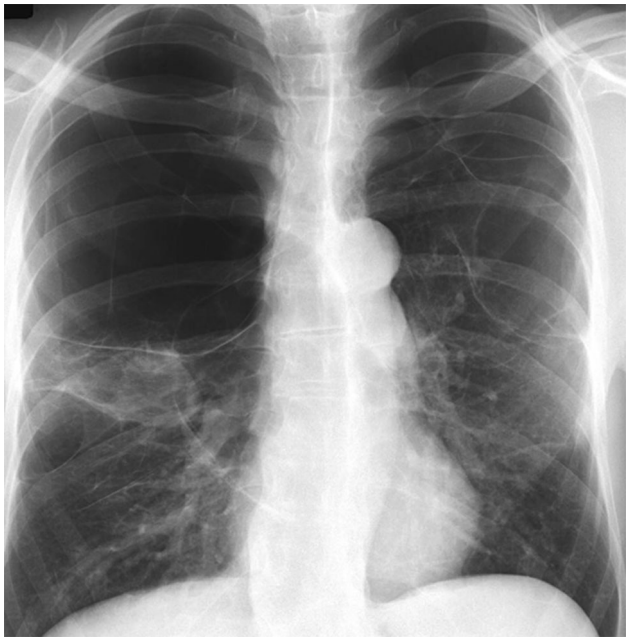

Fig. 1 Image of 'vanishing lung'

significantly increased risk of cervical cancer (RR = 1.4, CI 1.0–2.1). Their conclusion was that in non-smokers of tobacco cigarettes, marijuana use might affect certain site-specific cancers [41].

ASTHMA

There seems to be an increased risk of exacerbations in asthmatics who smoke cannabis. In an emergency room study [69] of patients presenting with an asthma exacerbation looking at those with cannabis use, they reviewed patients with at least one exacerbation in the last year and reduced lung function (FEV1 < 70%). There were more total exacerbations in the next 3 months (59 vs. 29%) in cannabis smokers compared with non-cannabis smokers as well as a higher rate of exacerbations (3.98 vs. 1.96/year).

COPD

As part of the Burden of Obstructive Lung Disease (BOLD) Initiative looking at a random sample of people over 40 in Vancouver, Canada, a questionnaire about tobacco and cannabis smoking was followed by spirometry [70]. Compared with non-smokers, tobacco-only smokers (but not cannabis-only smokers) experienced more frequent respiratory symptoms (odds ratio [OR] 1.50, 95% CI 1.05–2.14) and were more likely to have COPD (OR 2.74, 95% CI 1.66–4.52). Concurrent use of both cannabis and tobacco was associated with increased risk (even adjusted for age, asthma, and comorbidities) of respiratory symptoms (OR 2.39, 95% CI 1.58–3.62) and COPD (OR 2.90, 95% CI 1.53–5.51) if the lifetime dose of marijuana exceeded 50 marijuana cigarettes. The risks of respiratory symptoms and of COPD seemed to be related to a synergistic interaction between marijuana and tobacco, but did not occur in cannabis-only smokers. This may be related to the relative amounts of actual cigarettes used in the cannabis-only smokers being so much less, however.

ALLERGIC REACTIONS

Allergic reactions to the weed itself as well as cross reactivity to other allergens such as plant foods in the "cannabis-fruit/vegetable syndrome

[71]" are an underappreciated issue [72]. Hypersensitivity reactions [73] to MJ exposure and respiratory, contact, and ingestion can range from mild to severe, including anaphylaxis. This can be a result of protein allergens of the flower, fungal sensitization [74], or other components such as mold and pesticides [75]. While skin testing for the flower extracts (e.g., *Cannabis sativa*) are possible, these other factors can complicate the diagnosis.

OTHER LUNG COMPLICATIONS

Multiple case reports have been published of patients developing bullous disease from lung destruction associated with inhaled cannabis. Unfortunately for epidemiologic review, the cases are often those with combined inhalation of cannabis and cigarette smoke. Cases of large sometime multiple bullae, often with air fluid levels lead to scary looking radiographs and bad patient outcomes [76]. This is not something reported with tobacco alone, so the cannabis must be the causal factor.

Other case reports of cannabis-induced complications include hemoptysis [77], emphysema and secondary pneumothorax [78], hypersensitivity pneumonitis [79], eosinophilic pneumonitis [80], ARDS, vanishing lung syndrome (Fig. 1) [81], and emphysema [82, 83].

It is possible that the hyperinflation seen in cannabis users in addition to the Valsalva maneuver often used with inhalation may be involved in the cases of spontaneous pneumothorax and/or pneumomediastinum and of the peripheral apical lung bullae [50] that have been reported in isolated cases of marijuana smokers.

In addition, cases of aspergillosis have been reported [84] in cannabis smokers. Smoking marijuana affects the lungs structurally but may also affect them immunologically, by affecting alveolar macrophages [85]. This may predispose marijuana users to pulmonary infection. Both tobacco and marijuana are commonly contaminated with fungi, and serology from marijuana smokers exhibits evidence of *Aspergillus* exposure [86]. It remains to be seen whether fungal spores survive the burning process, leading to etiology related to inhalation and even potentially just handling.

CARDIOVASCULAR RISK

Marijuana use, mechanistically due to an increase in catecholamines, cardiac workload, and carboxyhemoglobin levels as well as episodes of significant postural hypotension, may trigger an increase in the risk of myocardial infarction, especially in older patients at risk for cardiovascular disease. In a study of 124 patients admitted for acute myocardial infarction [87] who reported marijuana use and controlled for other triggers, there was a 4.8-fold increase in the risk of myocardial infarction (95% confidence interval [CI] 2.4–9.5, p = 0.001) in the first hour following marijuana use as compared with periods of non-use.

Older data compared smoking a single cannabis cigarette to a tobacco cigarette. Smoking a cannabis cigarette showed an increase in the resting measurement of systolic blood pressure times heart rate of 54%, increased the venous carboxyhemoglobin level, and decreased the exercise time until angina by 50% in ten patients with angina pectoris. Compare that to the smoking of a single high-nicotine cigarette which increased the resting measurement of systolic blood pressure times heart rate by 36%, also increased the venous carboxyhemoglobin level, and decreased the exercise time until angina by 23%. As such, smoking either cannabis or high-nicotine cigarettes will decrease exercise performance until angina by increasing myocardial oxygen demand and by decreasing myocardial oxygen delivery. However, smoking one marijuana cigarette decreased the exercise time until angina greater than smoking a single high-nicotine cigarette ($p < 0.001$) [88].

Arrhythmias such as atrial fibrillation have been described in case studies, with other cases of fatal ventricular arrhythmias [89–92] also being described, postulated due to triggering of the Purkinje fibers or coronary vasospasm.

Transient cerebral ischemic events and strokes following marijuana use have also been reported [93–95]. Cerebral vasospasm is

postulated from a series of three patients with stroke symptoms and normal angiograms [96].

'Cannabis arteritis' [97] describes peripheral vascular consequences in high-dose marijuana users [32]. Disdier [98] described a series of ten patients who developed subacute and progressive ischemia of distal upper and lower extremities leading to tissue necrosis and gangrene [99].

OTHER INHALATIONAL METHODS OF INGESTION OTHER THAN SMOKING

For the most part, I have been discussing smoking cannabis. Clearly ingestion of cannabis orally is not going to have adverse respiratory effects but with most studies being done on whole marijuana smoke, it is difficult to determine if the currently available data is applicable to these newer products [100]. However, cannabis is inhaled in other vehicles including vaporizers, hookah (water pipe), and electronic cigarettes.

Waterpipe smoking tobacco has had claims of safety based on the lack of combustion and the water filter. These have been disproved, with CO levels shown to be higher than in cigarettes [101] (possibly related to the charcoal used to heat the tobacco; this is found in both tobacco and non-tobacco hookah smokers, which shows that the absence of tobacco does not make hookah smoking safe) and the fact that water does not filter out the harmful chemicals [102]. There is a paucity of data of smoking cannabis in a hookah, but safety cannot be assumed.

Vaporizers work by running air across the cannabis without actually burning or combusting it. With some types, the patient must inspire to allow the hot air to pass through the cannabis, which will expose the lungs also to the extreme heat and the risk of possible thermal damage. Other devices avoid the thermal exposure by blowing air into a different part of the vaporizer away from the heating element. The vaporizer contains cannabis vaporizer and thus raises cannabinoid levels but not exhaled CO levels. Switching from combustion to a vaporizer [103] has shown that users with respiratory irritation improved symptoms and lung function. As such, vaporizers may be of some value for cannabis users who want to avoid pulmonary problems and certainly offer a more rapid onset than do edibles. That being said, ensuring the correct vehicle is important with case reports of lung damage due to vaporizing cannabis oil [104].

Switching to vaporizer is therefore considered a safer method to using cannabis than smoking it [105]. Switching from smoking to vaping cannabis [106] has mostly just shown a reduction in symptoms of chronic bronchitis related to the smoking. Clearly removing smoking tobacco from the equation will also induce benefits. So, with some modest respiratory health benefits of vaping compared to smoking cannabis, this is likely the preferred delivery mechanism for those patients with chronic respiratory illnesses like asthma and COPD who wish to use cannabis for medicinal purposes [107] and require more rapid onset of effect than non-respiratory delivery systems like oral and topical.

EVALI or e-cigarette or vaping use-associated lung injury was first described in 2019 and led to a large reporting of cases. After publication of the problem, fortunately cases have declined sharply since August 2019 [108]. National and state data from patient reports and product sample testing show tetrahydrocannabinol (THC)-containing e-cigarette, or vaping, products, particularly from informal sources like friends, family, or in-person or online dealers, are linked to most EVALI cases and play a major role in the outbreak. Vitamin E acetate is strongly linked to the EVALI outbreak. One theory is that the vitamin E used as a thickening agent or to dilute THC oil in vape cartridges to make it go further was a part of the pathogenesis. Vitamin E acetate has been found in product samples tested by the FDA and state laboratories and in patient lung fluid samples tested by CDC from geographically diverse states. Vitamin E acetate has not been found in the lung fluid of people that do not have EVALI. It is now recommended to not add vitamin E acetate to any e-cigarette products, and the incidence of EVALI has thankfully fallen

significantly, to the point that the disease may be associated with the vitamin E and not the cannabis, but this is not yet completely clear. The bottom line is: vaping cannabis may not be a recipe for safe use!

CONCLUSIONS

Cannabis inhaled by combustion clearly leads to significant respiratory effects including changes in lung function (hyperinflation) and symptoms. The relationship with lung cancer is less clear. The equivalence of cannabis smoke exposure to cigarette smoke is also unclear, but the relationship shown in an earlier study still sounds like the best estimate I have seen; i.e., the 1:2.5–5 dose equivalence between cannabis joints and tobacco cigarettes for adverse effects on lung function [107].

For those purporting the benefits of cannabis, I am not saying it should not be used. Clearly, pregnant women and people under the age of 25 should be avoiding exposure due to potential adverse effects on developing brains and perhaps the risk of EVALI if vaporized in an electronic cigarette. In addition, almost all of the data collected are related to THC use, and with CBD being often recommended for management of multiple conditions, this is clearly an area in which research is required. That being said, when used, cannabis should be used safely without causing respiratory harm and should not be used combusted or combined with tobacco in a cigarette.

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