Clinic Rev Allerg Immunol (2019) 56:196–206
DOI 10.1007/s12016-017-8644-1

Cannabis-Associated Asthma and Allergies

J. M. Chatkin[1] · **L. Zani-Silva**[1] · **I. Ferreira**[2] · **N. Zamel**[3]

Published online: 18 September 2017

Abstract Inhalation of cannabis smoke is its most common use and the pulmonary complications of its use may be the single most common form of drug-induced pulmonary disease worldwide. However, the role of cannabis consumption in asthma patients and allergic clinical situations still remains controversial. To review the evidence of asthma and allergic diseases associated with the use of marijuana, we conducted a search of English, Spanish, and Portuguese medical using the search terms asthma, allergy, marijuana, marihuana, and cannabis. Entries made between January 1970 and March 2017 were retrieved. Several papers have shown the relationship between marijuana use and increase in asthma and other allergic diseases symptoms, as well as the increased frequency of medical visits. This narrative review emphasizes the importance to consider cannabis as a precipitating factor for acute asthma and allergic attacks in clinical practice. Although smoking of marijuana may cause respiratory symptoms, there is a need for more studies to elucidate many aspects in allergic asthma patients, especially considering the long-term use of the drug. These patients should avoid using marijuana and be oriented about individual health risks, possible dangers of second-hand smoke exposure, underage use, safe storage, and the over smoking of marijuana.

Keywords Asthma · Marijuana · Cannabis · Allergic diseases

✉ J. M. Chatkin
jmchatkin@pucrs.br

[1] Division of Respiratory Diseases, School of Medicine Pontificia Universidade Catolica do Rio Grande do Sul, Av Ipiranga 6680 Room 501, Porto Alegre 90610-000, Brazil

[2] Respirology Division, McMaster University, 399 Bathurst St, Toronto, ON M5T2S8, Canada

[3] Department of Medicine, Division of Respiratory Diseases, University of Toronto, 399 Bathurst St, Toronto, ON M5T2S8, Canada

Introduction

Cannabis is the most widely used illicit drug in the world, with users estimated at 120 to 250 million in 2014. Its prevalence of 2.6 to 5.0% of the adult world population has remained stable since 1998. About 3.8% of the global population used cannabis in 2014. This means that cannabis use in that year was about 27% higher than in 1998, as a consequence of the growth in the global population over the period [1, 2].

The highest use prevalence is found in North America (10.8%) and Oceania (10.9%), but it is consumed in almost all countries [2].

A comparison of the prevalence of cannabis use in the USA between the early 1990s and 2000s, evaluating more than 40,000 individuals, did not show a significant change and remained at around 4% in both decades. However, there was a significant increase in the rate of cannabis abusers, whose increase was 66% between the two surveys [3]. In 2014, a survey among individuals over 12 years of age, 8.4% reported cannabis use in the previous month, while 12.5% reported use in the previous year [4]. Kempker et al. [5], in a cross-sectional study involving nearly 7000 individuals, found that 59.1% of adults in that country reported that they had used cannabis in their lifetime and 12.2% in the previous 30 days.

Recently, Han et al. detected the decrease of current users of cannabis during the period 2005–2014, compared to 2002, among persons aged 12–17 years [6, 7].

The percentage of cannabis users has increased among individuals in the age group of 50 years or more, in parallel with

the aging of the American population, as is probably the case with many other countries. The prevalence of marijuana consumption in the previous year among individuals in the age group 50–64 years and those older than 65 years has increased by 57.8 and by 250%, respectively, between the periods 2006–2007 and 2012–2013 [7].

Another point to be considered in the prevalence of cannabis use is the influence of the legalization and decriminalization of this drug in some countries. There are initial reports showing an important increase of the prevalence of past-month cannabis use among general population in the USA and in some countries as Uruguay probably as a consequence of this new public health strategy (Fig. 1).

In Canada, about one third of university students reported cannabis use at least once, with percentages ranging very close to those of tobacco use. The prevalence of regular users was 14% each for both cannabis and tobacco, as per the 2009 report [8]. In that country, subjects aged 18 to 24 years were the group with the highest frequency of marijuana consumption [9]. The 2012 Canadian Community Health Survey–Mental Health (CCHS–MH) showed that 12.2% of Canadians aged 15 years or older (3.4 million individuals) had used marijuana in the past year. In that survey, 43% of Canadians reported that they had consumed it at some time in their lives, and 12% reported using it in the past year.

Prevalence data in South America is especially worrying in Argentina, Chile, Uruguay, and Brazil, all with frequencies higher than 8.0%. In this region, it is recognized that there is an important level of underreporting. [1]

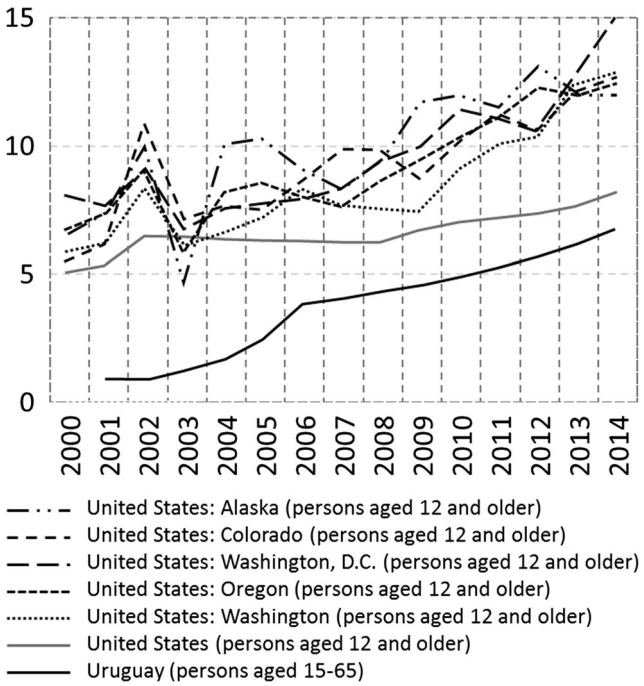

Fig. 1 Prevalence of past-month cannabis use among general population in the USA and Uruguay, 2000–2014. Adapted from [2]

Brazil is one of the Latin American countries with the highest cannabis registered consumption, currently ranging from 5 to 8% of people over 15 years, according to the states' evaluation [1, 10]. The recent survey II LENAD—National Survey of Alcohol and Drugs involved 4200 households in 14 municipalities with more than 1,000,000 inhabitants, as a representative sample of the Brazilian population. This survey estimated the prevalence of marijuana use in the previous 12 months at 3.4% among the adolescents and 2.5% for the adult population. In the same study, 4.3% of adolescents and 5.8% of the adult population reported use of marijuana at least once in their lives [11].

In Europe, the life-time estimates of cannabis use among adults range from 0.4% in Turkey to 22.1% in France [12]. In the UK, cannabis is the most commonly used illicit drug, with 6.5% of adults aged 16 to 59 years having used it in the last year (around 2.1 million people). Among younger adults aged 16 to 24 years, cannabis was also the most commonly used drug, with 15.8% having used it in the previous year (around 975,000 young adults). Spain registered the higher prevalence of use in this group (14.7%) [12–14] (Fig. 2).

Only about 10% of cannabis users seek specific treatment, probably due to the illegality of its use in the majority of the countries and to neurobehavioral alterations, including bias recall due to impaired memory. Consequently, the available statistics may be an underestimation of the actual numbers in most countries.

Another difficulty is the evaluation of the dose–response effect. There are many uncertainties in quantifying the use of cannabis, since there is a great variation in the amounts and strains of the plant included in each cigarette. In addition, there is a wide variety of methods in which cannabis is smoked, which alters the characteristics of the inhaled smoke and the health consequences.

Although several studies have been conducted over the years on the link between cannabis use and respiratory disorders, considerable controversies and conflicting findings still persist. The pulmonary complications of this illicit drug use

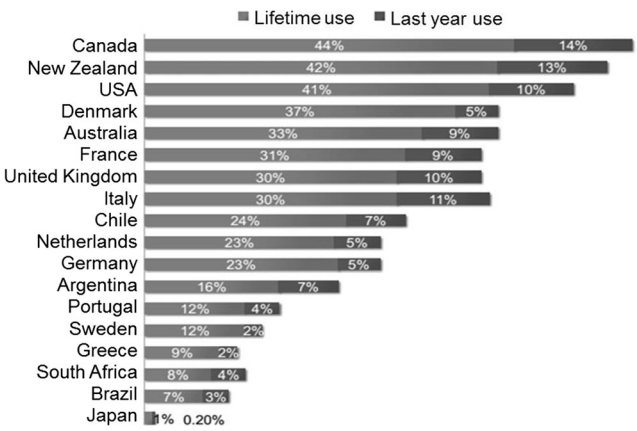

Fig. 2 Consumption of marijuana in some countries

may be the single most common form of drug-induced pulmonary disease worldwide.

Numerous clinical case reports have indicated the association between the use of cannabis with several chronic respiratory symptoms and many pulmonary diseases. These findings probably explain the reasons why cannabis users more frequently attend the outpatient health services. Since the consumption of cannabis is high, the health consequences of its short- and long-term use are frequently reviewed in the medical literature [5, 15–17].

However, the relationship between cannabis inhalation and asthma and allergies are complex and not easy to evaluate. Many years ago, cannabis was used to treat asthma symptoms for its mild bronchodilator effect, but more recently several studies have shown an association between inhalation of cannabis and worsening of asthma symptoms, more frequent exacerbations [18], and onset of new symptoms very compatible with asthma [15].

The prevalence of cannabis use in asthmatics has been reported in few papers. In a recent review, Self et al. [19] mention only six articles, the majority with very small number cases of asthma. Also, Martinasek et al. [20] in a systematic review of the respiratory effects of marijuana reported wheezing, shortness of breath, cough, and sputum, among other symptoms in a small number of manuscripts.

Some previous researches have suggested that adolescents with asthma smoke cannabis are more frequent than those without asthma [15, 21, 22].

Significantly, more American students with current asthma reported lifetime marijuana use (OR 1.3; 95% CI 1.1–1.6), marijuana use before age 13 years (OR 1.4; 95% CI 1.2–1.7), and current marijuana use (OR 1.3; 95% CI 1.1–1.6) compared to non-asthmatics. Further, those who had an asthma attack were significantly more likely to have tried marijuana before age 13 years (OR 1.9; 95% CI 1.4–2.7) [23].

Larsen et al. [24] analyzing data on marijuana use of the 2013 Ontario Student Drug Use and Health Survey concluded that adolescents with asthma had higher odds of smoking any type of substance cigarettes, water-pipes, and also marijuana as compared to non-asthmatics.

For this reason, the damage that can be caused by the use of marijuana on the respiratory system is recognizable and deserves a thorough analysis, not only because of the health implications derived from the high prevalence of illegal consumption, but also because its medicinal and recreational use is currently proposed in several countries [25, 26].

This paper aims to review the available literature on the relationship between cannabis use and asthma and other allergic manifestations, considering that this issue has not yet been fully clarified. The focus of this review does not include the legalization of medicinal and recreational use of cannabis, nor does it evaluates other recognized effects on the respiratory system or other organs and systems, as discussed in other papers [15–17, 27].

Smoking Cannabis

Cannabis sativa is a plant of the Cannabaceae family, containing more than 60 cannabinoids and over 400 other compounds. Cannabis enhances the sense of well-being modulating the response to stress, reward, and their interactions. Repeated use of cannabis may impair sensitivity to stress and reward. This effect, in vulnerable individuals, can lead to addiction and other adverse consequences [28].

Cannabis or marijuana consists of its dehydrated leaves and flowers, containing the active ingredient delta-9-tetrahydrocannabinol (9-THC). This chemical agent has psychoactive analgesic and relaxing properties. Other effects, such as antiepileptic, antiemetic, and soporific effects, are produced by cannabinol (CBN) and cannabidiol (CBD). These substances, especially THC, are at the center of the controversies over the use of this drug since their use for a long time has been proven to have numerous deleterious effects on human health, especially in the neurobehavioral area [25, 27–30].

THC can be inhaled as cigarettes (marijuana) or resin (hashish). It also can be vaporized, used orally, or applied to the skin or mucous membranes [31, 32].

Considering that the most frequent route of marijuana use is inhalational by the burning of *Cannabis sativa* leaves, there is a concern about the potential adverse effects to the lungs similar to tobacco burn. However, there are many differences between the tobacco and cannabis fumes [33].

The main difference between the composition of tobacco and cannabis smoke is that nicotine, the tobacco additive substance, is found only after the burning of tobacco leaves, whereas THC is the main psychoactive component of cannabis. THC and other substances as CBN and CBD are only found when burning marijuana. Both fumes have roughly similar amounts of volatile components (ammonia, hydrocyanic acid, and nitrosamines), but they are only qualitatively similar in relation to tar components (phenols, naphthalene, procarcinogenic benzopyrenes, and benzanthracene) [34]. Consequently, the presence of many substances with toxic potentials to the respiratory tract in both types of smoking raises the possibility of marijuana adverse effects in the respiratory system of the drug users [30, 35] (Table 1).

The methods of smoking cannabis or tobacco are different. Marijuana is smoked without filters and with smoke at higher temperatures than tobacco. Compared to tobacco users, cannabis users inhale larger volumes and more deeply, and then perform a prolonged Valsalva maneuvering. By doing this, they expect a larger and faster absorption of TCH to the central nervous system. The consequence of this maneuver is that the retention of tar and carbon monoxide is three and five times

Table 1 Components of marijuana and tobacco smoke (adapted from [34])

Component	Marijuana	Tobacco
Nicotine	–	2850
THC (μg)	820	–
CBN (μg)	400	–
CBD (μg)	190	–
Acetaldehyde (μg)	1200	980
Acetone (μg)	443	578
Acrolein (μg)	92	85
Ammonia (μg)	228	198
Acetonitrile (μg)	132	123
Benz(a)anthracene (μg)	75	43
Benzo(a)pyrene (μg)	31	22
Benzene (μg)	76	67
Carbon monoxide (ppm/cig)	2600	4100
Dimethylnitrosamine (μg)	75	84
Hydrogen cianide (μg)	532	498
Isoprene (μg)	83	310
Methylnitrosamine	27	30
m- and p-cresol (μg)	54.4	65
Naphthalene (μg)	3000	1200
o-Cresol (μg)	17,9	24
Phenol (μg)	76.8	39
Toluene (μg)	112	108

higher, respectively, than when smoking tobacco. This maneuver is probably responsible for the important increase of forced vital capacity (FVC) in some cannabis users [33, 36].

The frequency of use is also different between tobacco and cannabis. The average lifetime of the psychoactive components of marijuana is very long probably because of the body fat deposition. Just after consumption, an initial peak in concentration occurs in 4 to 10 min, whereas the more significant psychotropic effects last up to 2–3 h. However, serum detection occurs from days to several weeks after consumption. The bioavailability of cannabis components is quite heterogeneous, depending on the depth of inhalation and period of apnea, among other factors [33, 36].

THC was isolated in the mid-1960s, while the other components of the endocannabinoid system were identified in the last decades [29, 33]. The typical marijuana cigarette contains about 20 mg of THC, produced from 1 g of *Cannabis sativa* leaves, but also includes sometimes the whole plant, including the flowers, leaves, seeds, roots, and stems. These differences determine an important variation in potency of the drug. Cannabis consumed in the 1960s and 1970s contained 1 to 2% THC while the content currently marketed in several countries such as USA, New Zealand, UK, and Italy has a much higher average [2, 37–40]. In the USA, the potency of the illicitly produced cannabis increased from 4% in 1995 to 12% in 2014. The content of CBD, on the other hand, decreased from 0.28% in 2001 to < 0.15 in 2014 [37]. The average THC content in Japan currently can reach up to 22.6% in some samples. This high-potency cannabis preparation is usually known as "skunk" [39]. These more powerful preparations are developed by intentional isolation of female flowering plants at pollination, which increases the psychoactive properties by the higher THC content [41]. Hashish is another alternative to increase THC content and is prepared by scraping resin from the tops of the hemp plant. It contains five to ten times more THC per weight compared to marijuana [42].

Therefore, the consumption load (pack-years for tobacco cigarettes and joint-year for cannabis) to estimate health effects is not comparable among patients and among studies [29].

Cannabis Allergy

The description of cannabis allergy is sparse, although many authors agree that it may cause several reactions, including serious anaphylactic reactions.

The first report of allergic reaction to cannabis was published in 1971 describing a 29-year-old woman who after smoking marijuana for the first time presented symptoms compatible with an anaphylactic reaction. Positive skin tests and passive transfer studies confirmed the clinical diagnosis, and the author suggested an immunologic response to the THC [43].

It is now recognized that inhalation of cannabis pollen causes symptoms of allergic rhinitis (nasal congestion and sneezing) and conjunctivitis (pruritus and eye redness). It also may be linked to asthma (cough, wheezing, and dyspnea) discussed in another section of this manuscript [41] (Table 2).

Tessmer et al. [55] described 15 patients who, after inhalation of marijuana, had allergic manifestations such as rhinitis, conjunctivitis, sinusitis, periorbital angioedema, wheezing, and throat edema. One of their patients reported symptoms

Table 2 Allergic diseases associated with *Cannabis sativa.* Adapted from [41]

Allergies	references
Allergic rhinitis	[44–46]
Asthma	[21, 42, 45, 47, 48]
Allergic conjuntivitis	[44]
Eczema	[49]
Food allergy	[50]
Drug eruption	[51]
Contact urticaria	[52, 53]
Anaphylaxis	[49, 54]

compatible with anaphylaxis, such as anxiety, chest tightness, wheezing, abdominal cramps, and vomiting after ingestion of marijuana tea. Some of these individuals had also contact symptoms. They all had positive skin prick test. These patients reported recurrence of symptoms after further exposure and disappearance of the symptoms after cessation.

However, the immunological mechanisms related to exposure to *Cannabis sativa* components are not yet completely understood [41].

THC has been suggested as one of the allergens, and more recent studies showed type I hypersensitivity to high molecular weight proteins derived from *C. sativa*, ranging from 9 to 69 kDa [30, 31, 56–58].

Ocampo et al. [41] described in a 2015 review some molecules in *Cannabis sativa*, as possible allergens, mentioning THC, nonspecific lipid transfer protein (Can s 3), thaumatin-like protein, ribulose-1,5-biphosphonate carboxylase/oxygenase (RuBisCO), and oxygen-evolving enhancer protein (Table 3). However, the authors suggest caution, stating that there is still a need for more clear definition of pertinent allergens, develop a standardized extract, establish diagnostic sensitivity and specificity levels, and clarify treatment options for clinically affected cannabis-allergic patients.

It seems that the Can s3, the cannabis nonspecific lipid transfer (nsLTP), is one of the most important allergens, since it is present throughout the plant kingdom including fruits and vegetables [41, 57]. Consequently, the high variety of plant-derived food allergies among patients with a cannabis allergy might be explained by Can s3 sensitization. It also might explain cross-reactions to latex, alcoholic beverages, such as beer and wine and also tobacco. [52]

These several cross-reactions caused Ebo et al. [59] to propose a new clinical entity named "cannabis-fruit/vegetable syndrome." It links the sensitization to cannabis allergens and cross-allergies for latex, tomato, tobacco, fruits, and some alcoholic beverages. These cross-reaction allergies to cannabis and fruits are more commonly ascribed to peach, banana, apple, nuts, and orange [52] (Table 4).

Sensitized patients to pollen, tomato, latex, and tobacco may present allergy to cannabis, confirming a cross-reaction. Tobacco-sensitized users respond to challenge with purified marijuana leaf extract, confirming that cannabis produces allergic symptoms in such patients. Although tomato has cross-reactive allergens with cannabis, Larramendi et al. [61] informed that 72% of their patients admitted cannabis use, making definitive conclusions difficult.

The identity of most allergens from *C. sativa* remains unknown, and no allergens are currently listed by the International Union of Immunological Societies (IUIS) Allergen Nomenclature Sub-committee.

Sensitization can occur through respiratory inhalation, but also by skin contact and even oral ingestion, as mentioned before [49, 62]. Environmental exposure through the pollen as a plant aeroallergen has also been identified, and it is important in areas in USA, Southern Europe, and Central India [60].

In a study performed in Nebraska, USA, hay fever patients with hemp sensitivity proven by prick test had typical symptoms during cannabis pollination season [63]. In 1983, Freeman [64] showed that 70% of 129 unselected patients with positive atopy tests had also intradermal test or positive prick test for marijuana pollen and other allergens. Unfortunately, the authors did not collect information about the use of cannabis or specific exposure to *Cannabis* pollen.

Diagnosis of cannabis-related allergies is done by a specific anamnesis, and it is confirmed by skin prick tests. New tests are being introduced to improve the accuracy in diagnosis, such as the quantification of specific IgE antibodies, which is a fast and inexpensive method with high sensitivity and specificity 46, and basophil activation tests [52].

Armentia et al. [56] found that the skin test for cannabis extract presented high sensitivity (92.7%), but low specificity, possibly due to cross-reaction to plant allergens. In another study, 22% of 1000 patients showed positivity to the *Cannabis sativa* pollen test, but the association of clinical symptoms related to marijuana use was not adequately evaluated [65].

Nayak et al. [60], in a cooperative study conducted by the US Center for Disease Control and Prevention and University of Mississippi and the University of Toronto and the Gordon Sussman Clinical Allergy Research, both in Toronto, Canada, characterized IgE against extracts of the roots, leaves, flowers, and shoots in cannabis-sensitized patients, but the identification of many other allergens remains unknown.

It is unclear whether passive exposure to cannabis smoke has a potential to induce allergic sensitization. However, Decuyper et al. [66] observed a few cases of cannabis-related allergies in whom sensitization probably occurred via

Table 3 Potential allergens of *Cannabis sativa*. Adapted from [41]

Substance	References
Delta-9-tetrahydrocannabinol (THC)	[49]
Nonspecific lipid transfer protein (Can s 3)	[53, 55, 59]
Thaumatin-like protein	[58]
Ribulose-1,5-biphosphonate carboxylase/oxygenase (RuBisCO)	[59]
Oxygen-evolving enhancer protein 2	[60]

Table 4 Nonspecific lipid transfer protein ubiquity. Adapted from [52]

Fruits	Nuts	Beverages
Cherry	Hazelnut	Wine
Tangerine	Walnut	Beer
Orange	–	–
Peach	Others	–
Apple	Wheat	–
Tomato	Tobacco	–
Banana	Latex	–

passive exposure to cannabis. The suspicion was sustained by a thorough history (the patients denied any active use of the drug), skin prick test, basophil activation tests, total IgE, and specific IgE to several possible allergens.

Effects of Cannabis on Asthma

In the past, marijuana in low doses was considered useful to treat asthma because of its mild bronchodilator properties [67]. In contrast, there are now frequent reports showing its possible allergenic components and bronchial-constricting effects [30].

Soon after the 1971 Liskow's report mentioned before [43], Henderson et al. [42] in 1972 described 200 American soldiers stationed in West Germany with respiratory symptoms related to high doses of hashish. The subjects that used less than 25 g monthly more frequently reported sore throat, while those with the more severe manifestations, as bronchitis and asthma, consumed over 50 g per month. Symptoms included dyspnea, productive cough, and decreased exercise tolerance. Rhonchi, wheezes, and rales were found and the chest X-ray was normal. Vital capacity in these patients was decreased 15 to 40% below normal.

In 1973, two studies [36, 47] separately reported acute bronchodilation in asthmatic and normal individuals when smoking marijuana with controlled doses of aerosol or oral THC. Abboud and Sanders [68] reported in 1976 the same airway effect with oral THC in patients with asthma and healthy subjects. However, one of the asthmatics experienced severe bronchoconstriction, necessitating administration inhaled albuterol after the experiment. This patient had another episode of severe bronchospasm 1 week later on receiving oral THC again, requiring high dose of inhaled albuterol.

Cannabis sativa seed (CSS) is sometimes used for the production of vegetal oils and as feed for birds. This exposure probably explains the case report described in 1991 by Vidal et al. [69]. He reported a case of a 51-year-old man, bird breeder, with a history of extrinsic past asthma due to *Dermatophagoides pteronyssinus* sensitization. The subject developed rhinorrhea, chest tightness, dyspnea, cough, and wheezing, soon after exposure to hemp seeds, becoming asymptomatic 1 h later avoiding exposure. Clinical examination revealed diffuse expiratory wheezes in both lungs. Lung function tests revealed and demonstrated an obstructive pattern (FEV1/FVC 0.42). Prick test and intradermic tests with CSS extract were positive. A REIA (reverse enzyme immunoassay) and a release histamine test detected specific IgE against CSS. Bronchial challenge with CSS extract demonstrated FEV1 decrease of 31%. Control asthmatic subjects showed no alteration after bronchial challenge with the same extract.

Tetrault et al. [67] in 2007, in a systematic review, found 11 studies describing an acute bronchodilator effects due to short-term marijuana consumption. The studies that assessed long-term marijuana smoking and respiratory complications showed an association with increased respiratory symptoms, including cough, phlegm, and wheeze, findings that persisted after adjusting for tobacco smoking. However, no significant association was found between long-term marijuana smoking and changes in pulmonary function tests.

Other studies have confirmed mild and short bronchodilator effect of inhaled marijuana, including the reversal of methacholine-related or exercise-induced bronchospasms [70, 71].

This bronchodilator effect of marijuana is related to CB1 receptor stimulation in the postganglionic axons of the airway parasympathetic nerves, which inhibits the release of acetylcholine, thereby preventing the contraction of the bronchial muscles [5]. After this modest bronchodilator effect, there is a subsequent increase in airway inflammation, with the appearance of symptoms similar to chronic bronchitis. Regular or heavy cannabis consumption results in generalized airway inflammation, with evidence of respiratory epithelial cell injury and damage to the alveolar macrophages, increasing the frequency of pulmonary infections and the rate of asthma attacks [72].

However, it still remains to be determined whether there is a decrease or no effect in lung function [16, 67]. Pletcher et al. [73] described a relative preservation of FEV1 related to bronchodilator effect, compensating the inflammatory effects on the bronchial mucosa.

Another aspect to consider is that the decrease in the FEV1/FVC ratio in marijuana users seems to be caused by the increase in FVC [74]. Thus, the decrease in the Tiffeneau index after prolonged use of cannabis does not necessarily mean obstructive pulmonary disease, similar to that occurring in tobacco smokers. The preservation of FEV1 is probably a consequence of the above-mentioned bronchodilator effect of THC.

There is a dose-dependent effect of the use of inhaled cannabis on the respiratory tract [75]. This information is important because of the growing content of THC in marijuana marketed in many countries, as mentioned above. Despite the recognition of this dose-dependent effect, it is unknown

whether light but long-term users show an increased risk for asthma or COPD [76].

Compared to non-users, cannabis users have been reported to utilize emergency departments much more frequent due to respiratory problems, including asthma exacerbations, especially if they are also tobacco users [5, 8, 15, 18, 45]. However, most of the studies characterizing asthma patients according to frequency of emergency department visits have included tobacco smoke as a trigger, but not cannabis use.

Polen et al. [77] compared the 452 self-reported frequent users of marijuana who never smoked tobacco with 450 matched controls who reported they never smoked tobacco or marijuana. They found an increased risk of respiratory-related outpatient visits independent of tobacco smoking (RR 1.19 CI 95% 1.01–1.41). Interestingly, the risk of respiratory visits was significantly elevated for users for less than 10 years, but not for those who had smoked for 10 years or more. Contrary to expectations, among marijuana smokers, there was a negative association between duration of smoking and risk of visits for respiratory problems (p = .0002). The authors' hypothesis was that users with respiratory symptoms were more likely to quit smoking marijuana early in the process.

In a prospective case control design, Gaeta et cols [18] analyzed the association between substance abuse and emergency department visits for acute bronchospasm. They confirmed a significant association between inhaled substances of abuse (cocaine, opioids, and marijuana) and asthma exacerbation, although they could not establish a definite temporal sequence. ED admissions related to cannabis consumption increased in the last decade from 7.4 to 28% [56].

Besides those studies, several others have shown the association of smoking marijuana with worsening of asthma symptoms, such as wheezing, dyspnea, sputum production, and chest tightness [20, 22, 71, 75], and even acute exacerbations of asthma [8].

Allergic asthma caused by seasonal or occupational exposure to cannabis have also been described [69, 78], and some authors speculate that its use may be involved in some cases of eosinophilic pneumonia, although all reported cases were also positive for regular use of tobacco [41, 79].

A tobacco-controlled study from New Zealand showed that wheezing other than that caused by colds, exercise-induced shortness of breath, nocturnal wakening with chest tightness, and early morning sputum production were markedly more serious among cannabis-dependent patients. These symptoms were also more frequent (144, 61, 65, and 72%, respectively) when compared to non-users [80].

Compared to non-smokers, users of marijuana only, tobacco only, and both marijuana and tobacco showed significantly higher prevalence of chronic cough, sputum production, wheezing for at least 3 weeks a year, and more than two episodes of acute bronchitis; however, no statistically significant difference was found among the three groups of marijuana and tobacco users [81].

Combining marijuana with tobacco increases the known tobacco effects. However, with concurrent tobacco smoking, it becomes difficult to distinguish between changes due to cannabis and those due to tobacco.

Changes related to tobacco or marijuana use in peripheral airway function of 937 patients were studied in a longitudinal investigation in a population-based birth cohort. Using the impulse oscillometry system (IOS), the authors found that at age 38, cannabis use was associated with impairments in peripheral airway function, but only in women. Even with higher lifetime exposure, there was a weak association between cannabis and IOS findings in men. The findings related to tobacco use were similar to what have been published before. They concluded that tobacco and cannabis uses are associated with different patterns of spirometry and IOS abnormalities, probably affecting the bronchial tree at different airway generations with differences in susceptibility between sexes [82].

Second-hand inhalation of marijuana smoke still causes inhalation of toxic chemicals to the respiratory system, worsening symptoms [66].

Thus, asthmatics or those individuals with any form of bronchial hyperreactivity should avoid smoking marijuana.

Asthma Care in Cannabis Users

Marijuana users usually have higher rates of asthma exacerbations and other respiratory or allergic conditions. In addition, they do not achieve the expected rates of asthma control, despite visiting the emergency departments more frequent than non-users of illicit drugs.

Although not totally confirmed, the probable reasons for these findings are decreased compliance to treatment, irregular control of triggers, and choice of dangerous and inappropriate lifestyle [83].

Moreover, it is possible that clinicians, pulmonologists, and allergists despite including drug use or abuse in their anamneses, do not feel comfortable to treat these neuropsychiatric aspects.

Baxter et al. [84] showed that drug users, including cannabis consumers, receive less asthma care in outpatient clinics compared to non-drug user asthmatics. Later on, Baxter et al. published that among patients with substance-related disorders, the quality of asthma care may be of lower quality compared with patients with some other forms of mental disorders [85]. Therefore, they may be less likely to benefit from a well-organized treatment strategy. The authors suggest that this subgroup of asthmatics requires a different approach, probably integrating a multi-disciplinary treatment protocol.

In 2005, Hancox et al. noted that 1037 frequent cannabis users had significantly more morning cough (OR 1.97,

$p < 0.001$), sputum production (OR 2.31, $p < 0.001$), and wheeze (OR 1.55, $p < 0.001$). However, reduction of the marijuana consumption was associated with reductions in the prevalence of cough, sputum, and wheeze to levels similar to non-users [86].

Legalization and Decriminalization of Cannabis Use: Medicinal and Recreational Use

Cannabis use rates and the consequent medical problems, including the respiratory ones, are on the rise in parallel with the increase in the drug consumption in countries or areas where the use has been permitted. In addition, the higher potency of cannabis sold in both legal and illegal markets is spreading in many countries, which are further encouraged by a less punitive and more permissive legal attitude towards cannabis use with the decriminalization and legalization. Meanwhile, its use remains controversial since it is still illegal in most countries and legal or in the process of legalization in some others.

Legalizing the recreational use of cannabis means to allow the legal possession and use of the drug, while decriminalizing marijuana means to reduce the penalties for possession or use of small amounts to fines or civil penalties [87].

Most studies on the benefits of marijuana for these conditions have been inconsistent, except for those on pain management [87]. However, the medical disorders with the current best evidence that supports a possible benefit for cannabinoid use are multiple sclerosis in patient-reported symptoms of spasticity, multiple sclerosis central pain or painful spasms, multiple sclerosis bladder frequency, and chronic cancer severe pain/severe neuropathic pain. It is also allowed to be used in Alzheimer's disease, amyotrophic lateral sclerosis, cachexia/wasting syndrome, cancer, Crohn's disease, epilepsy and seizures, glaucoma, hepatitis C virus, human immunodeficiency virus/acquired immunodeficiency syndrome, and severe nausea and vomiting. Post-traumatic stress disorder is the sole psychological disorder for which medical marijuana has been allowed [87].

Medical cannabis users must be informed about acute central nervous system effects such as deficits in memory, judgment, attention, coordination, and perception (such as time and color), anxiety, dysphoria, and psychosis; chronic central nervous system effects such as cannabis use disorder, cognitive and memory deficits, and increased risk of psychosis; pulmonary effects; social dysfunction, such as in work/school; increased risk of motor vehicle accidents; and probably, an increased risk for acute cardiovascular event, especially in subjects with underlying heart disease [88].

Novel ways to manipulate the endocannabinoid system are being explored to maximize benefits of cannabinoid therapy and lessen possible harmful effects, resulting in a better risk/benefit ratio.

Its beneficial effects in these medical conditions give to the uninformed lay population the impression that it is a safe drug and does not cause major adverse effects. In addition, the promotion of its use by celebrities and movie or TV stars reinforce the permissive idea that youth and even the not-so-young individuals should enjoy life and the euphoria it produces, not valuing the frequent health risks [89].

Due to these reasons, it is possible that its use may become progressively more prevalent, and therefore, the possibility of allergic sensitization to any of the components of *Cannabis sativa* will be more frequent in the future. Cannabis may be an important allergen in young people, and the marijuana use should be investigated in every symptomatic young patient [57]. Polen et al. [77] reported that physicians notified marijuana use in the medical records of only 3% of the marijuana smokers, all of whom smoked daily or almost daily.

Another unsolved point is that vaping cannabis could mitigate the harmful effects of smoking cannabis to the lungs. Its proponents argue that burning the leaves at lower temperatures produces smaller amounts of toxic substances than the hot combustion of a marijuana cigarette. The health consequences specific to vaping cannabis preparations remain largely unknown due to the relative absence of studies.

Since the respiratory benefits of vaping compared to smoking cannabis are probably only modest, this recommendation is suitable only for patients with underlying severe respiratory disorders, such as asthma or COPD, wishing to smoke cannabis, but in whom smoking could worsen their respiratory symptoms [46].

This position is not opposed to the medicinal use of cannabis derivatives with proven scientific evidence or to those in development, but there is a need of well-designed randomized clinical trials with large samples to determine the actual medical benefits and adverse effects of marijuana. In addition, it is necessary to differentiate that use from recreational forms of consumption and demand that they follow the usual procedures for any drug.

Conclusions

The relationship between marijuana smoking and asthma remains complex. Marijuana was used as an alternative medicine to treat asthma symptoms for many years because of its mild bronchodilator properties, while its long-term use was known to be associated with increased respiratory symptoms. Considering that some reactions can be very serious, it is important to check for exposure to THC and the frequency to cannabis use in the clinical evaluation of an asthmatic or allergic patient. Studies on the immunological mechanisms and standardized reagents for diagnostic and clinical purposes are being developed, and probably, in the near future, new

tools will help health professionals deal with cannabis use [48].

The available evidence is not yet conclusive and many aspects need confirmation or further study. However, it is necessary for physicians to include in their daily practices research on marijuana use, especially among allergic young people. It should also be informed that recreational use is not without risks to health in general and the respiratory system in particular [26].

This review clearly shows that marijuana can induce allergic reactions with manifestation in various systems, especially in the respiratory system. Asthma, rhinitis, and aggravation of other symptomatic manifestations related to its use are being described, but the basic underlying mechanisms still need to be clarified [90].

Funding This manuscript received no grant.

Compliance with Ethical Standards

Conflicts of Interest The authors declare that they have no conflict of interest.

References

1. OEA—Organizacion Estados Americanos. Annual prevalence drug use by regions and globally by drug types. http://www.unodc.org/documents/wdr2014/Statistics/pdfInforme 2015; accessed Feb 3rd. 2017
2. United Nations Office on Drugs and Crime. World Drug Report 2016. United Nations publications, Sales No E 15 XI 6 2016;- https://www.unodc.org/documents/wdr2016/World_Drug_Report_2016.pdf
3. Compton WM, Grant BF, Colliver JD, Glantz MD, Stinson FS (2004) Prevalence of marijuana use disorders in the United States: 1991-1992 and 2001-2002. JAMA 291(17):2114–2121
4. Carliner H, Mauro PM, Brown QL, Shmulewitz D, Rahim-Juwel R, Sarvet AL et al (2017) The widening gender gap in marijuana use prevalence in the U.S. during a period of economic change, 2002–2014. Drug Alcohol Depend 170:51–58
5. Kempker JA, Honig EG, Martin G (2015) The effects of marijuana exposure on respiratory health in US adults. Ann Am Thorac Soc 12:135–141
6. Han B, Compton WM, Jones CM, Blanco C (2017) Cannabis use and cannabis use disorders among youth in the United States, 2002–2014. J Clin Psychiatry. https://doi.org/10.4088/JCP
7. Han BH, Sherman S, Mauro PM, Martins SS, Rotenberg J, Palamar JJ (2016) Demographic trends among older cannabis users in the United States, 2006-13. Addiction. https://doi.org/10.1111/add.13670
8. Tan WC, Lo C, Jong A, Xing L, Fitzgerald MJ, Vollmer WM et al (2009) Marijuana and chronic obstructive lung disease: a population-based study. CMAJ 180(8):814–820
9. Health Canada, Rotermann M, Langlois K (2013) Prevalence and correlates of marijuana use in Canada, 2012. Stat Can Health Rep 26(4):1–15
10. Fonseca AM, Galduróz JC, Noto AR, Carlini EL (2010) Comparison between two household surveys on psychotropic drug use in Brazil: 2001 and 2004. Cien Saude Colet 15(3):663–670
11. UNIFESP-Universidade Federal de São Paulo, INPAD-Instituto Nacional de Ciências e Tecnologias para Políticas Públicas do Álcool e outras Drogas. II Levantamento Nacional de Álcool e Drogas: Maconha (II LENAD-National Survey of Alcohol and Drugs). http://inpad.org.br accessed Jan 31, 2017 2017
12. Mounteney J, Griffiths P, Sedefov R, Noor A, Vicente J, Simon R (2016) The drug situation in Europe: an overview of data available on illicit drugs and new psychoactive substances from European monitoring in 2015. Addiction 111(1):34–48
13. European Monitoring Centre for Drugs and Drug Addiction. Perspectives on drugs: health responses to new psychoactive substances; models for the legal supply of cannabis. http://www.emcdda.europa.eu/topics/pods/legal-supply-of-cannabis 2016; accessed Nov 30, 2016
14. European Monitoring Centre for Drugs and Drug Addiction. Statistical Bulletin 2016. http://www.emcdda.europa.eu/ 2016
15. Caponnetto P, Auditore R, Russo C, Alamo A, Campagna D, Demma S et al (2013) Dangerous relationships: asthma and substance abuse. J Addic Dis 32(2):158–167
16. Tashkin DP (2013) Effects of marijuana smoking on the lung. Ann Am Thorac Soc 10(3):239–247
17. Volkow ND, Baler RD, Compton WM, Weiss SR (2014) Adverse health effects of marijuana use. N Engl J Med 370(23):2219–2227
18. Gaeta TJ, Hammock R, Spevack TA, Brown H, Rhoden K (1996) Association between substance abuse and acute exacerbation of bronchial asthma. Acad Emerg Med 3(12):1170–1171
19. Self TH, Shah SP, March KL, Sands CW (2016) Asthma associated with the use of cocaine, heroin, and marijuana: a review of the evidence. J Asthma. https://doi.org/10.1080/02770903.2016.1259420
20. Martinasek MP, McGrogan JB, Mayso A (2016) A systematic review of the respiratory effects of inhalational marijuana. Respir Care 61(11):1543–1551
21. Chatkin JM, Zabert G, Chatkin G, Zabert I, Jimenes-Ruiz C, Granda JI et al. Pulmonary disorders associated to marijuana consumption. Arch Bronconeumol 2017; [Epub ahead of print](doi: https://doi.org/10.1016/j.arbres.2017.03.019.)
22. Hublet A, De Bacquer D, Boyce W, Godeau E, Schmid H, Vereecken C et al (2007) Smoking in young people with asthma. J Public Health 29(4):343–349
23. Jones SE, Merkle S, Wheeler L, Mannino DM, Crossett L (2006) Tobacco and other drug use among high school students with asthma. J Adolesc Health 39:291–294
24. Larsen K, Faulkner GE, Boak A, Hamilton HA, Mann RE, Irving HM et al (2016) Looking beyond cigarettes: are Ontario adolescents with asthma less likely to smoke e-cigarettes, marijuana, waterpipes or tobacco cigarettes? Respir Med 120:10–15
25. Douglas IS, Albertson TE, Folan P, Hanania NA, Tashkin DP, Upson DJ et al (2015) Implications of marijuana decriminalization on the practice of pulmonary, critical care, and sleep medicine. A report of the American Thoracic Society Marijuana Workgroup. Ann Am Thorac Soc 12(11):1700–1710
26. Lutchmansingh D, Pawar L, Savici D (2014) Legalizing cannabis: a physician's primer on the pulmonary effects of marijuana. Curr Respir Care Rep 3:200–205
27. Volkow ND, Swanson JM, Evins AE, DeLisi LE, Meier MH, Gonzalez R et al (2016) Effects of cannabis use on human behavior, including cognition, motivation, and psychosis: a review. JAMA Psychiatry 73(3):292–297
28. Volkow ND, Hampson AJ, Baler RD (2017) Don't worry, be happy: endocannabinoids and cannabis at the intersection of stress and reward. Annu Rev Pharmacol Toxicol 57:285–308
29. Biehl JR, Burnham EL (2015) Cannabis smoking in 2015: a concern for lung health? Chest 148(3):596–606
30. Greydanus DE, Hawver EK, Greydanus MM, Merrick J (2013) Marijuana: current concepts. Front Public Health 42:1–17

31. Eisenberg E, Ogintz M, Almog S (2014) The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: a phase 1a study. J Pain Palliat Care Pharmacother 28(3):216–225
32. National Institute on Drug Abuse (NIDA). Marijuana abuse. https://www.drugabuse.gov/drugs-abuse/marijuana 2015; accessed in Feb 10, 2016
33. Wu TC, Tashkin DP, Djahed B, Rose JE (1988) Pulmonary hazards of smoking marijuana as compared with tobacco. N Engl J Med 318(6):347–351
34. Huber GL, First MW, Grubner O (1991) Marijuana and tobacco smoke gas-phase cytotoxins. Pharmacol Biochem Behav 40(3): 629–636
35. Turcotte C, Blanchet M-R, Laviolette M, Flamand N (2016) Impact of cannabis, cannabinoids, and endocannabinoids in the lungs. Front Pharmacol 7:317–323
36. Tashkin DP, Shapiro BJ, Frank IM (1973) Acute pulmonary physiologic effects of smoked marijuana and oral 9-tetrahydrocannabinol in healthy young men. N Engl J Med 289(7):336–341
37. ElSohly MA, Mehmedic Z, Foster S, Gon C, Chandra S, Church JC (2016) Changes in cannabis potency over the last 2 decades (1995–2014): analysis of current data in the United States. Biol Psychiatry 79(7):613–619
38. Murray RM, Quigley H, Quattrone D, Englund A, Di Forti M (2016) Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. World Psychiatry 15(3):195–204
39. Tsumura Y, Aoki R, Tokieda Y, Akutsu M, Kawase Y, Kataoka T et al (2012) A survey of the potency of Japanese illicit cannabis in fiscal year 2010. Forensic Sci Int 221(1–3):77–83
40. Wu HD, Wright RS, Sassoon CS, Tashkin DP (1992) Effects of smoked marijuana of varying potency on ventilatory drive and metabolic rate. Am Rev Respir Dis 146(3):716–721
41. Ocampo TL, Rans TS (2015) *Cannabis sativa*: the unconventional weed allergen. Ann Allergy Asthma Immunol 114:187–192
42. Henderson RL, Tennant FS, Guerry R (1972) Respiratory manifestations of hashish smoking. Arch Otolaryngol 95:248–251
43. Liskow B, Liss JL, Parker CW (1971) Allergy to marihuana. Ann Intern Med 75(4):571–573
44. Mayoral M, Calderon H, Cano R, Lombardero M (2008) Allergic rhinoconjunctivitis caused by *Cannabis sativa* pollen. J Investig Allergol Clin Immunol 18:73–74
45. Chopra GS (1973) Studies on psycho-clinical aspectsof long-term marihuana use in 124 cases. Int J Addict 8:1015–1026
46. Tashkin DP (2015) How beneficial is vaping cannabis to respiratory health compared to smoking? Addiction 110(11):1706–1707
47. Vachon L, FitzGerald MX, Solliday NH, Gould IA, Gaensler EA (1973) Single-dose effects of marihuana smoke. Bronchial dynamics and respiratory-center sensitivity in normal subjects. N Engl J Med 288(19):985–989
48. D'Souza DC, Ranganathan M (2015) Medical marijuana: is the cart before the horse? JAMA 313(24):2431–2432
49. Herzinger T, Schopf P, Przybilla B, Rueff F (2011) IgE-mediated hypersensitivity reactions to cannabis in laboratory personnel. Int Arch Allergy Immunol 156:423–426
50. Stadtmauer G, Beyer K, Bardina L, Sicherer SH (2003) Anaphylaxis to ingestion of hempseed (*Cannabis sativa*). J Allergy Clin Immunol 112:216–217
51. Ozyurt S, Muderrisoglu F, Ermete M, Afsar F (2014) Cannabis-induced erythema multiforme-like recurrent drug eruption. Int J Dermatol 53:22–23
52. Decuyper I, van Gasse AL, Cop N, Sabato V, Faber MA, Mertens C et al (2017) *Cannabis sativa* allergy: looking through the fog. Allergy 72(2):201–206
53. Gamboa P, Sanchez-Monge R, Sanz ML, Palacin A, Salcedo G, Diaz-Perales A (2007) Sensitization to *Cannabis sativa* caused by a novel allergenic lipid transfer protein, Can s 3. J Allergy Clin Immunol 120:1459–1460
54. Azofeifa A, Mattson ME, Schauer G, McAfee T, Grant A, Lyerla R (2016) National estimates of marijuana use and related indicators—National Survey on Drug Use and Health, United States, 2002-2014. MMWR Surveill Summ 65(11):1–28
55. Tessmer A, Berlin N, Sussman G, Leader N, Chung EC, Beezhold D (2012) Hypersensitivity reactions to marijuana. Ann Allergy Asthma Immunol 108(4):282–284
56. Armentia A, Castrodeza J, Ruiz-Muñoz P, Martínez-Quesada J, Postigo I, Herrero M et al (2011) Allergic hypersensitivity to cannabis in patients with allergy and illicit drug users. Allergol Immunopathol (Madr) 39(5):271–279
57. Armentia A, Herrero M, Martín-Armentia B, PeterRihs H, Postigo I, Martínez-Quesada J (2014) Molecular diagnosis in cannabis allergy. J Allergy Clin Immunol 2(3):351–352
58. Larramendi CH, Lopez-Matas MA, Ferrer A, Huertas A, Pagan J, Navarro L et al (2013) Prevalence of sensitization to *Cannabis sativa*: lipid-transfer and thaumatin-like proteins and relevant allergens. Int Arch Allergy Immunol 162:115–122
59. Ebo DG, Swerts S, Sabato V, Hagendorens MM, Bridts CH, Jorens PG et al (2013) New food allergies in a European non-Mediterranean region: is *Cannabis sativa* to blame? Int Arch Allergy Immunol 161(3):220–228
60. Nayak AP, Green BJ, Sussman G, Berlin N, Lata H, Chandra S et al (2013) Characterization of *Cannabis sativa* allergens. Ann Allergy Asthma Immunol 111:32–37
61. Larramendi CH, Carnes J, Garcia-Abujeta JL (2008) Sensitization and allergy to *Cannabis sativa* leaves in a population of tomato (*Lycopersicon esculentum*)-sensitized patients. Int Arch Allergy Immunol 146:195–202
62. Williams C, Thompstone J, Wilkinson M (2008) Work-related contact urticaria to *Cannabis sativa*. Contact Dermatitis 58(62):3
63. Maloney E, Brodkey M (1940) Hemp pollen sensitivity in Omaha. Nebr Med J 25:190–191
64. Freeman GL (1983) Allergic skin test reactivity to marijuana in the Southwest. West J Med 138:829–831
65. Abbas S, Katelaris CH, Singh AB, Raza SM, Ajab Khan M, Rashid M et al (2012) World Allergy Organization study on aerobiology for creating first pollen and mold calendar with clinical significance in Islamabad, Pakistan: a project of World Allergy Organization and Pakistan Allergy, Asthma & Clinical Immunology Centre of Islamabad. World Allergy Organ J 5(9):103–110
66. Decuyper I, Faber MA, Sabato V, Bridts CH, Hagendorens MM, Rihs HP et al. 2016 Where there's smoke, there's fire: cannabis allergy through passive exposure. J Allergy Clin Immunol Pract ; Epub ahead of print
67. Tetrault JM, Crothers K, Moore BA, Mehra R, Concato J, Fiellin DA (2007) Effects of marijuana smoking on pulmonary function and respiratory complications: a systematic review. Arch Intern Med 167(3):221–228
68. Abboud RT, Sanders HD (1976) Effect of oral administration of delta-tetrahydrocannabinol on airway mechanics in normal and asthmatic subjects. Chest 70(4):480–485
69. Vidal C, Fuente R, Iglesias A, Sáez A (1991) Bronchial asthma due to *Cannabis sativa* seed. Allergy 46(8):647–649
70. Grassin-Delyle S, Naline E, Buenestado A, Faisy C, Alvarez JC, Salvator H (2014) Cannabinoids inhibit cholinergic contraction in-human airways through prejunctional CB1 receptors. Br J Pharmacol 171(11):2767–2777
71. Moore BA, Augustson EM, Moser RP, Budney AJ (2005) Respiratory effects of marijuana and tobacco use in a US sample. J Gen Intern Med 20(1):33–37
72. Tashkin DP (2001) Airway effects of marijuana, cocaine, and other inhaled illicit agents. Curr Opin Pulm Med 7(2):43–61

73. Pletcher MJ, Vittinghoff E, Kalhan R, Richman J, Safford M, Sidney S et al (2012) Association between marijuana exposure and pulmonary function over 20 years. JAMA 307(2):173–181
74. Ribeiro LI, Ind PW. Effect of cannabis smoking on lung function and respiratory symptoms: a structured literature review. NPJ Prim Care Respir Med 2016; 26:doi https://doi.org/10.1038/npjpcrm.2016.71
75. Aldington S, Williams M, Nowitz M, Weatherall M, Pritchard A, McNaughton A et al (2007) Effects of cannabis on pulmonary structure, function and symptoms. Thorax 62:1058–1063
76. No authors listed (2017) Smoking marijuana and the lungs. Am J Respir Crit Care Med 195(3):P5–P6. https://doi.org/10.1164/rccm.1953P5
77. Polen MR, Sidney S, Tekawa IS, Sadler M, Friedman GD (1993) Health care use by frequent marijuana smokers who do not smoke tobacco. West J Med 158:596–601
78. Kumar R, Gupta N (2013) A case of bronchial asthma and allergic rhinitis exacerbated during cannabis pollination and subsequently controlled by subcutaneous immunotherapy. Indian J Allergy Asthma Immunol 27:143–146
79. Sauvaget E, Dellamonica J, Arlaud K, Sanfiorenzo C, Bernardin G, Padovani B et al (2010) Idiopathic acute eosinophilic pneumonia requiring ECMO in a teenager smoking tobacco and cannabis. Pediatr Pulmonol 45:1246–1249
80. Taylor DR, Poulton R, Moffitt TE, Ramankutty P, Sears MR (2000) The respiratory effects of cannabis dependence in young adults. Addiction 95:1669–1677
81. Tashkin DP, Coulson AH, Clark VA, Simmons M, Bourque LB, Duann S et al (1987) Respiratory symptoms and lung function in habitual heavy smokers of marijuana alone, smokers of marijuana and tobacco, smokers of tobacco alone, and nonsmokers. Am Rev Respir Dis 135(1):209–216
82. Robinson PD, King GG, Sears MR, Hong CY, Hancox RJ (2017) Determinants of peripheral airway function in adults with and without asthma. Respirology 22(6):1110–1117
83. Weitzman ER, Ziemnik RE, Huang Q, Levy S (2015) Alcohol and marijuana use and treatment nonadherence among medically vulnerable youth. Pediatrics 136(3):450–457
84. Baxter JD, Samnaliev M, Clark RE (2008) Patterns of health care utilization for asthma treatment in adults with substance use disorders. J Addict Med 2(2):79–84
85. Baxter JD, Samnaliev M, Clark RE (2009) The quality of asthma care among adults with substance-related disorders and adults with mental illness. Psychiatr Serv 60(1):43–49
86. Hancox RJ, Poulton R, Ely M, Welch D, Taylor DR, McLachlan CR et al (2010) Effects of cannabis on lung function: a population-based cohort study. Eur Respir J 35(1):42–47
87. Belendiuk KA, Baldini LL, Bonn-Miller MO (2015) Narrative review of the safety and efficacy of marijuana for the treatment of commonly state-approved medical and psychiatric disorders. Addict Sci Clin Pract:10(10)
88. Schrot RJ, Hubbard JR (2016) Cannabinoids: medical implications. Ann Med 48(3):128–141
89. Whiting PF, Wolff RF, Deshpande S, Di Nisio M, Duffy S, Hernandez AV et al (2015) Cannabinoids for medical use: a systematic review and meta-analysis. JAMA 313(24):2456–2473
90. Tashkin DP (2014) Increasing cannabis use: what we still need to know about its effects on the lung. Respirology 19(5):619–622