Marijuana and lung diseases

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Purpose of review
Cannabis sativa (marijuana) is used throughout the world, and its use is increasing. In much of the world, marijuana is illicit. While inhalation of smoke generated by igniting dried components of the plant is the most common way marijuana is used, there is concern over potential adverse lung effects. The purpose of this review is to highlight recent studies that explore the impact upon the respiratory system of inhaling marijuana smoke.

Recent findings
Smoking marijuana is associated with chronic bronchitis symptoms and large airway inflammation. Occasional use of marijuana with low cumulative use is not a risk factor for the development of chronic obstructive pulmonary disease. The heavy use of marijuana alone may lead to airflow obstruction. The immuno-histopathologic and epidemiologic evidence in marijuana users suggests biological plausibility of marijuana smoking as a risk for the development of lung cancer; at present, it has been difficult to conclusively link marijuana smoking and cancer development.

Summary
There is unequivocal evidence that habitual or regular marijuana smoking is not harmless. A caution against regular heavy marijuana usage is prudent. The medicinal use of marijuana is likely not harmful to lungs in low cumulative doses, but the dose limit needs to be defined. Recreational use is not the same as medicinal use and should be discouraged.

Keywords
chronic obstructive pulmonary diseases, lung cancer, marijuana smoking

INTRODUCTION

Marijuana has been used by man for over 3000 years [1–3]. It has been used by multiple civilizations. Its uses have ranged from utilitarian (rope) to medicinal to religious. In the United States, marijuana was used medicinally until 1941, when it was dropped from the United States Pharmacopeia [1–3]. The Controlled Substances Act passed in 1970 classified marijuana as a schedule 1 drug, defined by the Drug Enforcement Administration as follows (http://www.justice.gov/dea/druginfo/ds.shtml): 'Schedule I drugs, substances, or chemicals are defined as drugs with no currently accepted medical use and a high potential for abuse. Schedule I drugs are the most dangerous drugs of all the drug schedules with potentially severe psychological or physical dependence'. This definition persists to this day.

Marijuana is the most commonly used illicit substance worldwide. Globally, the estimated prevalence of marijuana users in 2011 was 180.6 million or 3.9% of the adult population aged 15–64 years [4]. Though the United States, Australia and New Zealand reported the highest prevalence of cannabis use, it is produced and consumed in virtually every country and territory of the world [4]. Marijuana is derived from the cannabis plant belonging to the Cannabaceae family [4,5]. It is prepared from the dried flowering tops and leaves of the female plant [4,5]. Combustion of marijuana produces hundreds of substances. The main psychoactive ingredient in marijuana is delta-9-tetrahydrocannabinol (THC); however, more than 60 compounds (cannabinoids) have been identified within the cannabis plant [5,6]. An endogenous cannabinoid (endocannabinoid or eCB) system is a recently discovered signaling system comprising the cannabinoid CB1 and CB2 receptors [5].

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KEY POINTS

- There is unequivocal evidence that habitual or regular marijuana smoking is not harmless and causes respiratory symptoms and airway inflammation.
- Occasional use of marijuana with low cumulative use is not a risk factor for the development of COPD.
- A caution against regular heavy (and likely moderate) marijuana use is prudent as data on long-term effects of heavy use of marijuana on the lung are sparse and conflicting.
- Medicinal use of marijuana is likely not harmful to lungs in low cumulative doses.
- Recreational use should be discouraged based on current evidence, particularly in young individuals, because of both injury to the user and potential injury to others via cognitive and psychomotor defects.

The most common route of marijuana use is by inhalation of smoke. Smoke is usually inhaled from compacted and rolled leaves, analogous to a cigarette (a 'joint'), or from a water pipe ('bong') [6]. Most studies quantify exposure to cannabis smoke as 'joint-years'; one joint-year is equivalent to one joint smoked daily for a year. When marijuana is smoked, THC is absorbed into the bloodstream via the lungs [6,7]. Marijuana smoke contains a complex mixture of chemicals qualitatively similar to tobacco smoke with the exception of nicotine, which is unique to tobacco [8,9]. As it shares similar compounds with tobacco smoke, increasing widespread use of marijuana smoking raises concerns for short and long-term respiratory complications including bronchitis, pneumothorax/pneumomediastinum and chronic lung diseases like chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD) and lung cancers. This review highlights the recent studies that explore the use of marijuana and its impact on the respiratory system. There are direct implications for both recreational and medical use of marijuana.

EFFECTS OF SHORT-TERM AND LONG-TERM MARIJUANA SMOKING ON LUNG FUNCTION: DOES IT CAUSE CHRONIC OBSTRUCTIVE PULMONARY DISEASE?

Although the effects of marijuana smoking (both short-term and long-term) on lung function have been assessed by many studies for over 40 years, the bronchodilator properties of cannabis were likely known and were used for treating asthma in the late 1800s [2,10]. In fact, as noted, cannabis was listed in the United States Pharmacopeia from the mid-19th century until 1941, predating scientific studies by over a century [2,10]. It is interesting that Tashkin *et al.* [11] and Vachon *et al.* [12] were the first to demonstrate bronchodilator properties of cannabis in young healthy individuals and published study results in the same medical journal in the same year. Tashkin *et al.* [13,14] subsequently reported a similar bronchodilator effect of cannabis in patients with mild asthma as well as in patients with methacholine and exercise-induced bronchospasm. A systematic meta-analysis by Tetrault *et al.* [15] assessing acute effects of marijuana smoking found consistent association between short-term marijuana administration and bronchodilation [such as increases of 0.15–0.25 l in forced expiratory volume in 1 s (FEV_1), peak flows, and airway conductance].

Multiple studies have also evaluated the long-term effects of marijuana on lung function and compared lung function in marijuana smokers with that in tobacco smokers. One of the first studies to assess long-term effects of marijuana smoking on lung function was published in 1972 by Henderson *et al.* [16] and showed decreased vital capacity in marijuana smokers. These initial data were subsequently contradicted. Many cross-sectional and longitudinal studies published since then were systematically analyzed in a meta-analysis by Tetrault *et al.* [15] in 2007. On analysis of 14 studies, the authors found no consistent association between long-term marijuana smoking and airflow obstruction measures [as defined by decreased FEV_1 and FEV_1/forced vital capacity (FVC) ratio]. Since the publication of the meta-analysis, one cross-sectional and three longitudinal (observational cohort) studies of long-term effects of marijuana smoking on lung function have been published (Table 1).

Aldington *et al.* [17] published a comparative study of the effects of marijuana and tobacco in 2007. The authors performed high-resolution computed tomography (HRCT) of the chest and pulmonary function testing on 339 individuals (75 marijuana-only smokers, 91 smokers of both marijuana and tobacco, 92 tobacco-only smokers, and 81 nonsmokers) in New Zealand. The study results showed no significant change/decline in FEV_1 or FEV_1/FVC ratio in marijuana smokers. There was also no evidence of emphysema on HRCT, although marijuana use was associated with an increased percentage of low-density lung tissue both on the apical slice [odds ratio (OR) 3.3] and the mean of the three slices (OR 2.4), suggestive of hyperinflation.

A similar lack of association between marijuana smoking and airflow obstruction has also been reported in the Dunedin birth cohort study [19].

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Table 1. Effects of use of marijuana alone on lung function measures in comparison with nonsmoking patients in most recent epidemiological studies

Lung function measure	Aldington *et al.* (2007) [17]	Tan *et al.* (2009) [18]	Hancox *et al.* (2010) [19]	Pletcher *et al.* (2012) [20▪▪]
FVC	↑	↑	↑	↑
FEV_1	↔	↔	↑	↑
FEV_1/FVC	↔	↔	↔	↔
TLC	↔	NP	↑	NP
RV	↔	NP	↔	NP
DLco	↔	NP	↔	NP
sGaw	↓	NP	↓	NP
Raw	↑	NP	↑	NP

↑, Increase; ↓, decrease; ↔, no association; NP, not performed.
DLco, diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FEV_1/FVC, ratio; FVC, forced vital capacity; Raw, airway resistance; RV, residual volume; sGaw, specific airway conductance; TLC, total lung capacity.

Lung function was assessed in participants of the longitudinal Dunedin Multidisciplinary Health and Development Study in New Zealand. Spirometry was performed periodically at each assessment from age 9 until age 32. After adjusting for tobacco exposure, cannabis was not associated with lower FEV_1 values or lower FEV_1/FVC ratios, but was associated with significantly higher FVC, higher airways resistance (Raw) and lower specific airway conductance (sGaw) (Table 1).

The most recently published cohort study with an extended follow-up period of 20 years used data from the Coronary Artery Risk Development in Young Adults (CARDIA) subjects, and found no airflow obstruction in occasional or low cumulative marijuana smokers [20▪▪]. There was an expected decrease in FEV_1 and FVC in tobacco smokers, with linear dose–response relationship. Interestingly, the authors found statistically significant nonlinearity in marijuana smokers, with increases of both FEV_1 and FVC at low levels of exposure (up to 7 joint-years of lifetime exposure) followed by decreases in FEV_1 at higher levels of exposure. Although limited by a small proportion of heavy marijuana users (1%) in the study population, the results do suggest a possibility of airflow obstruction with heavy marijuana use and warrant caution until further studies are performed.

Most people who smoke marijuana also smoke tobacco [21]. The combined effect of both on lung function and COPD was reported by Tan *et al.* [18] in a population-based cohort study of 878 people in Vancouver as part of the Burden of Obstructive Lung Diseases (BOLD) study. The concurrent use of marijuana and tobacco was associated with increased risk (compared to tobacco use alone) of COPD [OR 2.90, 95% confidence interval (CI) 1.53–5.51] when the lifetime dose of marijuana exceeded 50 marijuana cigarettes, suggesting synergy between marijuana and tobacco. There was no association between smoking only marijuana and COPD, although, as noted by the authors, the study had insufficient power to detect a modest association.

On the basis of the above studies, it is evident that occasional use of marijuana with low cumulative use is not a risk factor for the development of COPD. The heavy use of marijuana alone may possibly lead to airflow obstruction, and marijuana in combination with tobacco may be synergistic for COPD. Additional longitudinal studies are needed to confirm these findings. It is important to note that the majority of the studies have several limitations such as difficulty in obtaining accurate information for an illicit drug, quantifying its use, and small proportions of marijuana-only smokers (even smaller numbers of very heavy users). Yet another confounding fact is that the study inclusion criteria for marijuana use varied from 50 joints over a lifetime to more than 40 joint years (>10 000 joints in lifetime).

RESPIRATORY SYMPTOMS IN HABITUAL MARIJUANA SMOKERS

Despite conflicting results and apparent lack of association between marijuana smoking and COPD, almost all studies analyzed in a recent meta-analysis have confirmed increased respiratory symptoms in marijuana smokers (alone or in combination with tobacco) when compared to nonsmokers [16]. Habitual marijuana smokers report a wide range of symptoms that include cough, wheeze, shortness of breath, sputum production, chest tightness, pharyngitis, hoarse voice, and worsening asthma symptoms [16].

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In the US National Health and Nutrition Examination Survey (NHANES III) study, both marijuana and tobacco smokers had increased likelihood of respiratory symptoms [21]. Current marijuana use was defined as self-reported 100+ lifetime uses and at least 1 day of use in the past month. When adjusted for tobacco use, age, gender and current asthma, ORs for respiratory symptoms in the 414 marijuana users (mean age 31.2 years) versus 4789 nonsmokers (mean age 41.5 years) were 2.00 (95% CI 1.32–3.01) for chronic cough, 1.89 (95% CI 1.35–2.66) for chronic phlegm, and 2.98 (95% CI 2.05–4.34) for wheezing. The most striking observation of this study was the fact that marijuana users had rates of respiratory symptoms comparable to those of tobacco smokers who were 10 years older. Consistent results have been reported in recent observational cohort studies as well [17–19], proving that marijuana smoking is associated with increased respiratory symptoms.

Respiratory symptoms in marijuana smokers are likely due to injurious effects of marijuana smoke on the bronchial mucosa. Fligiel *et al.* [22] demonstrated large airway inflammation on endobronchial biopsy specimens of habitual marijuana smokers. The histopathologic abnormalities reported were goblet cell hyperplasia, loss of ciliated epithelial cells, and intra-epithelial and sub-epithelial inflammation; the authors concluded that smoking of marijuana alone caused at least as extensive histopathologic abnormalities in the tracheo-bronchial mucosa as tobacco alone, including metaplastic changes and nuclear alterations that could be premalignant. In another study [23] using videobronchoscopy and mucosal biopsy, tracheo-bronchial inflammatory changes were demonstrated in healthy (relatively asymptomatic) habitual marijuana smokers. Visual bronchoscopic inspection found significantly higher bronchitis index scores (based on central airway erythema, edema, and airway secretions) in marijuana-only smokers, tobacco-only smokers, and in combined marijuana/tobacco smokers, as compared to nonsmokers. These significant inflammatory changes were confirmed on bronchial biopsies. This study demonstrated that marijuana use (with or without tobacco) causes large airway inflammation/injury; the authors speculate that routine physical examination and spirometry may be insensitive measures of lung injury caused by cannabis in asymptomatic smokers.

Whether these histopathologic changes are reversible on marijuana smoking cessation is yet to be proven. However, the benefit of marijuana smoking cessation with respect to the resolution of pre-existing symptoms of chronic bronchitis has been demonstrated in a recently published study by Tashkin *et al.* [24▪▪]. A total of 299 out of 446 subjects who were participants of a longitudinal cohort study were followed over a mean of 9.8 years and showed significant symptom resolution/improvement on marijuana smoking cessation. The authors noted that communicating these findings might help motivate habitual smokers of marijuana to quit for symptom relief.

MARIJUANA AND LUNG CANCER

Considering the unequivocal causal relationship that exists between tobacco smoking and lung cancer, there is a valid concern that smoking of marijuana may be a risk factor for lung and other cancers as well. Many earlier studies have shown that marijuana smoke contains qualitatively many of the similar chemicals (carcinogens and co-carcinogens) as tobacco smoke [8,25]. Moir *et al.* [9] extensively examined the chemical composition of both mainstream and side-stream smoke from marijuana and tobacco cigarettes and showed qualitative similarities between the two, with some quantitative differences. In addition, histopathologic and immunohistologic evidence in marijuana users, including bronchial squamous metaplasia and overexpression of molecular markers of pretumor progression, suggests biological plausibility of marijuana smoking as a risk factor for the development of lung cancer [22,26,27].

Taking this evidence a step further, Maertens *et al.* [28▪] employed a toxicogenomics approach and used murine lung epithelial cells to compare and contrast the toxicological molecular pathways affected by marijuana smoke condensate (MSC) and tobacco smoke condensate (TSC). Both TSC and MSC exposure was associated with the expression of genes involved in xenobiotic metabolism, oxidative stress, inflammation, and DNA damage response. It is interesting that the MSC was more potent than TSC in dose–response analyses for most common pathways. The data clearly demonstrate that the pathways affected by MSC are similar to those with TSC. This study has strengthened the link supporting the biological plausibility of marijuana smoking as a risk factor for the development of lung cancer.

Current epidemiologic evidence linking marijuana smoking and lung cancer is sparse [17,29,30]. In addition, the epidemiologic studies on marijuana are subject to confounding by concomitant use of tobacco, and limited by small sample sizes, young age of participants and, most important, underreporting [31]. A pooled analysis of case–control studies in Tunisia, Morocco, and Algeria found that the OR for lung cancer was 2.4 (95% CI 1.6–3.8)

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for cannabis smoking after adjusting for lifetime tobacco pack-years [32], raising concerns of oncogenicity.

The most recently published population-based Swedish cohort study gains strength both from being the largest study to examine this association (49 321 men aged 18–20 years) and from including an extended follow-up period [33▪▪]. The authors reported that heavy cannabis smoking (defined by lifetime use of more than 50 times for their study) was associated with more than a two-fold risk of developing lung cancer over a 40-year follow-up period [33▪▪]. This study bolstered the previous small epidemiologic study results that found a positive association between marijuana smoking and lung cancer. Although it has been difficult to establish a conclusive link between marijuana smoking and cancer development epidemiologically, available evidence definitely warrants caution against regular heavy (and possible moderate) marijuana use.

EMPHYSEMATOUS BULLAE, BAROTRAUMA (PNEUMOTHORAX), AND INTERSTITIAL LUNG DISEASE IN MARIJUANA SMOKERS?

Beshay *et al.* [34] observed an unusual increase in the number of young patients at their surgical emergency unit in Switzerland who presented with pneumothorax and history of marijuana smoking. They analyzed and reported their observations as the first and largest case series of spontaneous pneumothorax in heavy marijuana smokers [34]. They were also the first to introduce the term 'joint years' to quantify marijuana smoking. The radiographic findings on chest computed tomography (CT) scan showed large apical bullae, up to12 cm in size, which were not present in controls (patients with pneumothorax and no history of marijuana smoking) over the same time period (2002–2004). In a recent review, 36 case reports of apical bullous lung disease attributable to heavy cannabis smoking have been reported in young adults [10]. It is evident that marijuana smokers tend to have deeper inhalations and hold their breath for up to four times longer than cigarette smokers, sometimes accompanied by valsalva maneuvers which may predispose them to barotrauma [35]. It has been postulated that this smoking technique (rather than cannabis itself) is responsible for cases of spontaneous pneumothorax and bullous lung disease reported in young marijuana smokers [10,34,35]. However, considering the widespread use of marijuana but only few case series of apical bullae and pneumothorax reported in the literature, it is obvious that these changes are rare complications, if at all, of marijuana smoking.

Marijuana smoking has been shown to cause interstitial changes in lungs of primates [36], but we found no studies showing such effects in humans. Fligiel *et al.* [36] reported interstitial fibrosis in 24 rhesus monkeys inhaling marijuana on autopsy. It is interesting though that interstitial changes have been reported in a marijuana smoker and attributed to talc contamination of marijuana joints, a known cause of pneumoconiosis and interstitial changes [37▪].

MEDICINAL USE AND NONPULMONARY ADVERSE EFFECTS OF MARIJUANA

A detailed discussion of nonpulmonary adverse effects as well as medicinal use of marijuana is beyond the scope of our review. However, we will briefly touch on some of them as they are all germane to the issue of marijuana use. Marijuana and other cannabinoids (including synthetic cannabinoids) are modestly effective in symptom palliation in cancer patients [38▪]. One of the earliest recognized indications for cannabinoids was chemotherapy-induced nausea and vomiting [39]. The available literature suggests that it is also effective in alleviating pain related to cancer, especially neuropathic pain [38▪,40▪]. Marijuana stimulates appetite in patients with AIDS-related wasting, but has minimal effect in cancer patients with anorexia [38▪]. Interestingly, in experimental tissue culture studies, cannabinoids have been found to have antitumorogenic activities in numerous studies [41–44,45▪]. Despite these preclinical data for cannabinoid-mediated antitumor activity dating back as far as 30 years, we found only one small clinical (a pilot phase I trial) study published in the English literature [46]. The primary endpoint of this study was to assess safety of intracranial THC administration in nine refractory glioblastoma patients. Cannabinoid delivery appeared to be well tolerated, but all nine patients died (as expected from underlying glioblastoma) and the median survival was 24 weeks from the beginning of cannabinoid administration.

On our literature review, there is no evidence that recreational cannabis use improves general health. The main acute adverse effects in marijuana users include tachycardia, anxiety, and panic, especially in occasional or naive users [47,48]. Marijuana can be considered to be addictive, and is especially so when individuals start using it in their teens [48]. Marijuana smoking can lead to impairment of cognition, coordination, and judgment and can result in automobile accidents [49,50▪]. A systematic review of high-quality studies by Asbridge *et al.* [51▪▪] concluded that acute

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cannabis consumption nearly doubles the risk of a collision resulting in serious injury or death. Data suggesting long-term harmful effects of cannabis on neuropsychological function are emerging [52▪]. A recently published Dunedin study in which individuals were followed from birth to age 38 years concluded that persistent cannabis use is associated with neuropsychological decline broadly across several domains of functioning [53▪▪].

CONCLUSION

The use of marijuana represents a complex issue. Marijuana has been used throughout the world for thousands of years. Our understanding of its biochemical spectrum has led to a sort of 'justification' for this long-standing multicultural valuation of the drug. We know that different components help (or may help) us in the treatment of nausea, anorexia, chronic pain, depression, and possibly cancer. The legal vilification of marijuana has put those who wish to prescribe or to use it in conflict with the law and has made it difficult to explore its potential benefits. Any toxicity of marijuana pales when compared with the greatest legalized killer in the world today – tobacco.

Yet marijuana is a mind-altering drug. Its usage leads to psychomotor impairment. Chronic usage may lead to neurocognitive deficits. A subset of chronic users will continue to use marijuana even when it has a negative impact upon social function and productivity, a reasonable definition of addiction. Youth are particularly susceptible. These facets of usage have similarity to some of the sequelae of alcohol consumption, and, akin to alcohol, it is more than reasonable to protect our youth from marijuana and to try to limit usage in any context in which usage may lead to harm to others.

The inhalational route of acquisition of drugs is extremely efficient, as it bypasses filtration and carries products which can be absorbed across the capillary membranes directly to the brain. When combustion is used to micronize those products, a large number of particles are generated which have no known benefit and which can potentially cause harm. Sorting out the hundreds of products of combustion and their impact (negative or positive) upon the respiratory system has been a barrier in the study of marijuana and of tobacco products. Skipping the 'fine print', it is obvious that the inhalation of smoke has the potential for irritation and injury to lungs and bronchi. While different cultures have used the inhalation of different combustion products for thousands of years, we can be seen as a society of excesses; if something is smoked occasionally, it may lead to no or minimal harm, whereas constant chronic usage may lead to injury.

Current data indicate that the inhalation of combusted marijuana is indeed a respiratory irritant. It can cause symptoms of cough, phlegm, and wheeze. On the other hand, marijuana appears to function as a bronchodilator, and there are no data at present to link the use of marijuana alone with COPD. There are data to support synergistic injury if marijuana is used in conjunction with cigarettes. There is some evidence that heavy marijuana use can cause cancer (and some experimental evidence that some components of marijuana have efficacy against some cancers).

There are two 'solutions' to the issues noted above. The first is to offer marijuana in noncombustible forms when the plant is perceived to be of medical benefit. The second, already proceeding, is to identify and isolate components of the plant with specific benefits and make those components available in known quantities and delivered by routes which do not cause collateral harm.

In summary, there is unequivocal evidence that habitual or regular marijuana smoking is not harmless and causes respiratory symptoms. A caution against regular heavy (and likely moderate) marijuana is prudent because of both injury to the user and potential injury to others via cognitive and psychomotor defects. Medicinal use of marijuana is likely not harmful to lungs in low cumulative doses. Recreational use is not the same as medicinal use and should be discouraged based on current evidence, particularly in young individuals.

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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