MAEDICA – a Journal of Clinical Medicine
2022; 17(4): 911-920
https://doi.org/10.26574/maedica.2022.17.4.911

MAEDICA - a Journal of Clinical Medicine

REVIEW

Cannabis – a Rewritten History and Its Pulmonary Consequences

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ABSTRACT

Cannabis presents itself as another challenge of the last decade. Better and better deciphered through in-depth studies, this drug remains a source of scientific debates. Legalized in some states, it competes with tobacco regarding the effects generating respiratory symptoms, chronic bronchitis, bronchial cancer, respiratory infections, etc. In this article we will review the pharmacology, epidemiology, clinical and prevention aspects and try to demonstrate which of these are the most effective means of prevention. This review proves once again that this drug has many hidden dangers.

Keywords: cannabis, smoking, lung diseases.

INTRODUCTION

Usually referred to as "marijuana", cannabis is one the most common news prime-time subjects as illegal activities. Although prohibited in most countries, its consumption is exceeded only by that of tobacco. *Cannabis sativa*, an annual wind-pollinated plant which is widely known as 'Marijuana', seems to be for many a "friendly plant" with multiple historical uses for medicinal and recreational purposes (1). Also, this plant has a long history – it was the oldest cultivated crop plant (fossils discovered already 12000 years ago) (2). Even if it is mainly known for the hallucinogenic effects obtained through consumption, we meet cannabis in multiple areas of everyday life, such as in construction materials (cement-concrete), textile fibers, cellulose and paper, food through seeds and oils, medicines, cosmetics, etc (3). This plant was used for the first time in 2727 BC, in China (4); traditional Chinese medicine used its seeds to treat constipation, malaria, rheumatic pains as well as labor childbirth. Around the year 1530, a Spanish named Pedro Quadrado won a labor grant to undertake the cultivation of cannabis in Mexico, and it took almost 40 years until its production, sale and recreational use, and later, export was banned. Over the years, cannabis highlights a multifaceted role as a valuable therapeutic agent due to the phytochemicals it contains, playing an important role in the prevention and treatment of various diseases, including pain release, anxiety, epilepsy, glaucoma, multiple sclerosis, post-chemotherapy symptoms, HIV/AIDS symptoms, sleep disorders, bowel diseases, and

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Article received on the 25th of August 2022 and accepted for publication on the 19th of December 2022

many others. Smoking marijuana, a custom of Mexican soldiers before its banning (5), refers to some parts of the plant cannabis, for example rolling a join, which is achieved by drying the flowers and leaves of female hemp, but it also has important uses in many other fields (6). Concerning our interest in the impact on respiratory health, there is a lack of data regarding the safety of cannabis smoking. Due to the increasing use and controversial background, the United Nations voted to remove cannabis used for medicinal purposes from the category of the world's most dangerous drugs in December 2020 (7). While cannabis remains illegal in most countries, several countries are considering decriminalizing or legalizing its use, but unfortunately all discussions are only focusing on mental and social health effects.

Chemical components of cannabis; pharmacology

Cannabis can be split into thousands of different strains, dozens of categories, and several different species that share multiple qualities, but also developed significant differences, which help them survive in different climates. There are three main well-known types of cannabis plants: *Cannabis sativa*, *Cannabis indica* and *Cannabis ruderalis*. Pharmacologically active compounds, particularly cannabinoids and terpenes, are excreted by trichomes, the glandular hairs of cannabis. Terpenes are compounds that create the smell and taste of a plant. Delta-9-THC and cannabidiol are the two major psychoactive compounds, which can be found in varying concentrations. The composition of cannabis is complex, including a variety of compounds that belong to almost all of biogenetic classes such as cannabinoids, alkaloids, flavonoids, terpenoids, steroids, fatty acids, amino acids, etc (8). Cannabis includes a long list of compounds and acts as polypharmacy with a rich diversity of nutritionally and pharmaceutically important metabolites. Phytochemical constituents, cannabinoids, and their derivatives are considered to have therapeutical roles. Seeds and other parts of the plant have different concentrations of active metabolites. Not only cannabinoids are of interest in plant biosynthetic capacity, but also non-cannabinoid compounds like lignanammides, prenylated flavonoids, and stilbenoid derivatives, stand out for their protective role against various types of pathogenic attacks (8). Many possible actions are described. Among the 26 flavonoids isolated from cannabis, researchers associated inhibitory roles of lipoxygenase to kaempferol, apigenin, vitexin, isovitexin, cannflavin A, B, luteolin, and quercetin; cyclooxygenase blocking activity shows potential in interrupting the process of carcinogenesis – chemoprevention (9). A variety of biologically active metabolites has been described as existing in this plant and many researchers have worked extensively on the complex biosynthetic pathways of these phytochemicals, their synergistic effects, isolation, as well as characterization and medicinal benefits (10).

Two major psychoactive compounds, delta-9-THC and cannabidiol, which have now higher concentrations than 50 years ago due to selective breeding, are responsible for the euphoria and relaxation effects but also for the negative side effects like psychosis, anxiety, etc (11). Pharmacologically active ingredients, including tetrahydrocannabinol (THC) and cannabidiol (CBD), are the most studied components *in vitro*, on models. The effects of cannabinoids compounds on human body are based on the mechanism of engaging the cannabinoid receptors, parts of the endocannabinoid system. CB1 receptors, belonging to the G-protein coupled family (identified in 1988), are expressed mainly in the brain, but also in the lungs, liver and kidneys. The CB2 receptor is expressed mainly in the immune system, in hematopoietic cells and in parts of the brain, originally described in differentiated myeloid cells, showing 44% amino acid homology with CB1 but a distinct, though similar, binding profile. There are five classes of cannabinoid compounds with activity on receptors, with minor selectivity for the agonists delta-9-THC and cannabidiol, but major selectivity (>1000-fold) and nanomolar affinity shown by antagonists (12). There are numerous ingesting methods, including inhalation, oral, sublingual and atopic. The fastest delivery way is by inhalation, smoked without a filter as joints with cannabis leaves, or mixed with tobacco in spliffs, but also vaporizing by water bongs (13).

Epidemiological aspects

The amplitude of cannabis consumption is difficult to imagine. In 2018, a US national survey on drug use and health estimated that, starting from 2002, the number of current marijuana smokers aged ≥12 years had grown from 6.2% to 10.1% (14). And this is far from being the top of the

iceberg. In 2001, among US secondary school students in the 12th-grade, 19% smoked cigarettes, 5.8% marijuana, and 3.6% consumed alcohol daily (about 49% of the 12th-grade students have smoked marijuana at some point in their life and about 29.5% have been smoking marijuana in the past months) (15). Major concerns about the public health impact of cannabis use have also arisen in Europe. Between 2010 and 2019, the past-month prevalence of cannabis use increased by 27% among European adults (from 3.1 to 3.9%) (the biggest increase being identified in the sample of 35–64-year-olds). The rate of treatment entry for cannabis problems *per* 100,000 adults increased from 27.0 (95% CI 17.2 to 36.8) to 35.1 (95% CI 23.6 to 46.7) (16). Moreover, it is estimated that more than 40% of the current users smoke cannabis on a daily or near-daily basis (17). Marijuana acts as a 'gateway drug', which drives them toward ingesting more illicit compounds such as cocaine or heroin (18), with the initiation in the smoking of marijuana typically being placed at the beginning of adolescence and young adulthood. This is the reason why two-thirds of new marijuana smokers belong to the age range of 12–17 of youth, whereas the remaining third is composed of young adults in the age range of 18–25 (19); 36–44% of consumers smoked only tobacco, 3% in each study smoked only marijuana, and 16–17% had smoked both tobacco and marijuana. Of all marijuana smokers, over 80% had also smoked tobacco (20). During the COVID-19 pandemic, 6.8% reported an increase in cannabis vaping since the pandemic started, 37.0% quitting or reducing vaping in general, and 42.3% no change. Participants were more likely to report an increased cannabis vaping if they perceived "Vaping is safer than smoking cigarettes (21). The majority of consumers remain cannabis smokers. One example is coming from Canada; data shows that smoking (79%) was the most common method of cannabis consumption, followed by eating it in food (52%), vaporizing using a vape pen or e-cigarette (24%), and vaporizing using a vaporizer (12%) (22). Concerning the risk of emergency room (ER) visits and hospitalizations, this was significantly greater among cannabis users than among control individuals, and respiratory-related reasons were the second most common cause for ER visits and hospitalizations in the all-cause outcome (23).

Pathogenic actions of cannabis in the lungs

Although cannabis has a multitude of beneficial effects that health researchers are trying to exploit, we still identify a negative impact of its consumption, like epithelial hyperplasia, cellular disorganization, cell atypia and fibrosis (24, 25). Smoke from marijuana can also negatively affect B and T lymphocytes, and NK cells and can also alter the expression of many cytokines, which are involved in immunological respiratory defense mechanisms (26). We also have confirmations from *in vitro* studies that cannabinoids have demonstrated immunosuppressive properties and profibrotic effects (27, 28). Other effects are in relation with the decrease in the recruitment of inflammatory cells, the suppression of cytokines, and an overall improvement in mortality (29). *In vivo*, in the epithelial cells of the lungs, there are no cannabinoid receptors; however, CB1 receptors have been identified in the nerve endings of the airways and (30) both CB1 and CB2 receptors in eosinophils, monocytes, and monocyte-derived macrophages (31). CB1, CB2, and TRPV1 are identified "*in situ*" and "*in vitro*" at the protein level in airway epithelial cells (32).

Tobacco *versus* cannabis

Marijuana and tobacco are often associated in terms of their way of consumption and effect on the brain. Tobacco smoking is considered to be the previous stage of cannabis ingestion. Although viewed as a whole, they may have common characteristics, but a granular approach highlights major differences between them, from the parts of the plant that are consumed and the method of inhalation to the constituent substances and their mode of action. Researchers report that a tobacco smoker inhales 4,350 compounds *vs* only 2,575 in a cannabis smoker. It is worrying that the tobacco compounds which are known to have adverse health risks through carcinogenic, mutagenic, or other toxic mechanisms are also common in cannabis, counting 69. (33). Tar is common for both, but there is a lack of nicotine in cannabis products and a lack of tetrahydrocannabinol (THC), while there is a trace amount of THC-like constituents (cannabinoids) in tobacco products (34). This means that marijuana is carcinogenic, as it consists of compounds named polycyclic aromatic hydrocarbons such as benzo[a]pyrene, a key factor that induces cancer in human lungs (35). Lack of filters in marijuana cigarettes brought

a two-fold more inhaling tar than that of tobacco, *per* unit weight in addition to the same profile of smoke (36). In the same time, it is a difference in breathing and puff volume. In marijuana, the depth of smoke after inhalation is 40% greater, and the holding time of breath is four times stretched in contrast to the characteristics of tobacco smoke (with delivery and retention of a four-fold excessive amount of tar in the lung by marijuana smoke) (37). This has certain consequences. Marijuana smoking involves techniques that expose users to carbon monoxide and tar deposition at a chance 3–5 times higher than tobacco smokers, and the incidence of airflow obstruction caused by marijuana smoking was equivalent to 2.5–5 times of that caused by tobacco smoking (38, 39). Finally, comparing marijuana injuries with those of tobacco has many similarities when smoke is inhaled deeply without filtering and when it is held for a longer time in the lungs (1).

"Benefits" of cannabis on lung – an eternal discussion

Phytochemicals identified in *Cannabis sativa* are described in some studies as having beneficial effects. Orientin, vitexin, isovitexin, quercetin, luteolin, kaempferol, apigenin from the cannabis flowers, seedlings and fruits are effective in experimental studies with a role in carcinogens detoxification and enzyme activation (40). Denbinobin is found in all components of the plant and has antiproliferative activity (41). Cannflavins A, B, and C, from the sprouts and flower buds, have antimicrobial and antileishmanial activity (42) and cannabidiol from plant has anticancer activity (43). Other possible effects, including acting as a cellular antioxidant and the antimutagenic activity, are coming from caffeoyltyramine, cannabisin A, B, C, and x-6 linoleic acid, which are found in seeds and sprouts (44). The list of experimental effects is much longer. Studies show that the endocannabinoid system regulates cell division and proliferation, apoptosis, necrosis, and autophagy, proposing cannabinoids and their agonists as complementary pharmacological agents in the treatment of lung cancer (45). Other studies have also discovered supplementary effects. Recently, heterogenous extracts of *Cannabis sativa* female flower have been found to induce the death of lung cancer A549 cell line in a time-dependent manner but at very low doses (50–900 ng/mL), following induction of early apoptosis, cell cycle arrest, elevation of ROS level, and activation of caspase 3 (46). The mechanism seems to be mediated by the binding to the CB2 receptors, since their blockage caused attenuation of *Cannabis sativa* effects on A549 cells (46). Due to their anti-metastatic activity, studies report that cannabinoids induce the process of decreasing secretion of plasminogen activator inhibitor-1 (PAI-1) (47) and upregulation in the expression of ICAM-1 (48, 49).

Coronary Artery Risk Development in Young Adults (CARDIA) study, a longitudinal study collecting repeated measurements of pulmonary function and smoking over 20 years (26th of March 1985 – 19th of August 2006) in a cohort of 5115 men and women in four US cities (50), concluded that, although frequent marijuana smokers had more outpatient medical visits for respiratory problems, dosage seemed to be the key to health outcomes, with low cumulative marijuana not being associated with adverse effects on pulmonary function. Marijuana exposure shows non-linear pulmonary function ($P < .001$): at low levels of exposure, FEV (1) increased by 13 mL/joint-year (95% CI, 6.4 to 20; $P < .001$) and FVC by 20 mL/joint-year (95% CI 12 to 27; $P < .001$), but at higher levels of exposure, these associations leveled or even reversed. In a cross-sectional study of 7,716 US adults from the National Health and The cohort of the Nutrition Examination Study, Kempker (51) obtained the pulmonary function inflection threshold value as 20 joints-year, so that for smokers below this value it showed no effect on FEV_1/FVC, but for those who exceeded this threshold there was a 2.1-fold risk for the FEV_1/FVC\70% ratio, represented by a significant increase in FVC and no significant reduction in FEV_1. The differences between tobacco and marijuana may be related to dosing but may also include the anti-inflammatory effect of the last one. The lung transfer factor for carbon monoxide has also been reported to only be reduced in smokers of cannabis and tobacco. Other interesting data concerning marijuana use within 0–4 days of lung function measurement shows a 13% reduction in exhaled nitrous oxide, though the clinical manifestation of this acute effect is unknown (52). As already proven, at least experimentally, THC mediates the acute bronchodilator effect of inhaled cannabis (53).

At the same time, arguments have been proved that suggested that the endocannabinoid

system had an input in the state of sleep. Also, THC mediates in a dose-dependent manner, associating sleep changes with slow waves, which are important aspects for the cognitive function of learning and memory consolidation. With so many sleep disorders, there is a common assumption among marijuana users that cannabis may also improve sleep status, but thematic studies have contested this theory, especially on long time use. THC can yield a biphasic effect on sleep, on low dosages decreasing the time to sleep onset and higher dosages increasing it, but also demonstrated a reduction in total rapid eye movement (REM) sleep and REM density (54). National Academies of Sciences, Engineering, and Medicine researchers conclude that in individuals with sleep disturbance associated with conditions like obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and multiple sclerosis, cannabinoids, primarily nabiximols, are an effective treatment to improve short-term sleep outcomes (55). Thus, cannabinoids could have a role in treating sleep disorders.

Deleterious lung effect of marijuana

Respiratory symptoms like cough, sputum production, and wheezing are increased in current chronic users of cannabis (53), which may cause chronic bronchitis but with no certain evidence of shortness of breath or irreversible airway damage like concurrent tobacco smokers. By comparison, giving up cannabis consumption results in a significant improvement in respiratory status by reducing wheezing, morning cough, and the amount of sputum; moreover, 10 years follow-up shows no predisposition to an increased risk of developing chronic bronchitis (53).

There are controversial results concerning asthma and cannabis consumption (56), with half of the studies favouring this association (57) and the others not supporting the relation of the drug with asthma bronchiale (58). It is clear that this relationship between marijuana smoking and asthma should be further clarified (59). Older studies report that the physiologically active bronchodilator compound in marijuana, Δ9-tetrahydrocannabinol, is responsible for a small bronchodilator effect, to cause a reversal of methacholine-related or exercise-induced bronchospasms in asthma patients, and may have therapeutic potential (60, 61). Overall effects of marijuana are strongly related to dosage and exposure timing, so that only 2% THC in a single "joint" could trigger an acute bronchodilation in healthy subjects (62) and in patients with mild asthma, with a rapid onset and duration of at least two hours. It is important not to forget that consuming cannabis implies exposure to pollens, a well-known risk factor for asthma exacerbations. A three-month follow-up highlights a 30% higher rate of exacerbation in cannabis smokers *versus* non-cannabis smokers (63). Controversial effects are also described for COVID-19 infections, due to its negative impact on the respiratory and vascular systems, reducing the production of cytokines, which affects the users' immune system and increases the susceptibility to infection and progression of COVID-19. Cannabinoid acids from hemp, cannabigerolic and cannabidiolic acid, prevented infection of human epithelial cells by a pseudovirus expressing the SARS-CoV-2 spike protein and prevented the entry of live SARS-CoV-2 into cells. Studies have suggested the use of cannabinoids in the prophylaxis and treatment of COVID-19, due to their anti-inflammatory effect. High-cannabidiol (CBD) cannabis extracts attenuated angiotensin-converting enzyme 2 (ACE2) and transmembrane serine protease 2 (TMPRSS2) expression and the induction of inflammatory mediators cyclooxygenase-2 (COX2), IL-6, and IL-8 *via* the protein kinase B (AKT) pathway, highlighting their potential anti-COVID-19 features (64). *in vitro*, on the murine model, cannabichromene (CBC) was able to reverse hypoxia (increasing blood O2 saturation by 8%), ameliorate the symptoms of ARDS (reducing the pro-inflammatory cytokines by 50% in the lungs and blood), and protect the lung tissues from further destruction (65). The action of cannabis remains duplicative concerning viral and bacterial infections. At the same time, it increases the progression and severity of the infection, but it seems promising to modulate the immune system (66).

In 2019, in a more commercial than well-intentioned attempt to shift the attention of tobacco users to trendier products such as e-cigarettes and vaping products, an epidemic of pulmonary lung illness broke out in US. Tetrahydrocannabinol (THC), the naturally occurring THC isomer found in the cannabis plant, was associated with the majority EVALI products. Different unnatural THC isomers will be encountered also in other THC-containing products observed in the vaping products (67).

Smoking cannabis has similar effects to those of tobacco. It can lead to pulmonary edema with hemorrhage (68). The consequences of inflammation in the large airway include bronchitis symptoms and resistance to the increased airway. Obstruction of airflow occurring while breathing and the appearance of emphysema at the same time are described in some studies (69). Daily, excessive coughing and phlegm synthesis can induce severe chest pain, which causes obstruction during breathing and makes users prone to lung infection (70). Cough, sputum production, and wheezing are present in a 3:5 ratio among cannabis smokers (71). In comparison with tobacco, components of cannabis are more cytogenic, highly mutagenic, and have a high tendency to cause damage to chromosomes (70). There are other symptoms or effects like severe bronchitis, pneumonia, recurrent synthesis of phlegm, breathlessness, frequent gasping, and production of chest sound even without having a cold (72). Like in tobacco, frequent cannabis smokers present the same clinical picture associated with symptoms of cough, sputum production and wheeze, but it is important to notice that quitting tend improve the overall health status, indicating that inflammation of the airway caused by cannabis may be largely reversible (73).

Marijuana is carcinogenic, with its compounds named polycyclic aromatic hydrocarbons such as benzo[a]pyrene being a key factor for the progress of cancer in the human lungs (35). Histological tests of biopsied bronchial samples from marijuana users demonstrated a predisposition to premalignant changes (53). In 2013, Callaghan *et al* reported a two-fold increased risk of lung cancer among marijuana smokers *versus* non-smokers after 40 years, but although the cohort study comprised a significant number of subjects, almost 50 000 army conscripts, the study was limited only to smoking history assessed at the time of conscription (74). For other researchers, cannabis seems not to be carcinogenetic; various factors might contribute, e.g., potential anti-inflammatory and anti-neoplastic properties of THC and other cannabinoids (75). Bronchial biopsies have demonstrated that marijuana users showed not only manifest airway inflammation but also histopathological and/or molecular changes indicative of precancerous bronchial activity (76).

Long-term cannabis use is known to impair large airway function, leading to airflow obstruction and hyperventilation (77). Inducing edema and inflammation, 3-4 marijuana cigarettes have similar histological effects as 20 tobacco cigarettes (25). This could be one of the explanations for COPD or emphysema lesions. "Marijuana lung" consists of apical emphysema with large bullae formation, specifically in younger patients (78, 79). Direct toxicity of marijuana components and airway barotrauma could be an explanation for another possible complication – pneumothorax. In an attempt to obtain the maximum effect of the psychoactive substances in cannabis, the user approaches breath-holding techniques employed during smoking, resembling a Valsalva maneuver, techniques that precipitate barotrauma increasing bulla formation and predisposing to pneumothorax. Cannabis usage is associated with primary spontaneous pneumothorax (PSP) recurrence and the eventual need for surgery. Cannabis users (n = 28; 42%) had a higher rate of tobacco use (79 *vs.* 38%; p = 0.005), lower BMI [21.0 kg/m^2 (IQR 18.3–23.1) *vs.* 22.2 kg/m^2 (IQR 19.9–28.6), p = 0.037] and were more likely to require intervention at first presentation than non-marijuana users (80). Hyperinflation and its impact on lung function are explained by another study. The findings of the long-running Dunedin Multidisciplinary Health and Development Study, which has documented the use of cannabis and measured lung function throughout adult life up to age 45 in more than 1000 individuals born in Dunedin in 1972/73, brought some other evidence related to marijuana use (81). The authors found an increased large-airway resistance and lower mid expiratory airflow; impairment of FEV_1/FVC ratio was because of higher FVC. Higher values for total lung capacity (TLC), airway resistance (Raw) and alveolar volume (Va), and lower values for specific airway conductance (sGaw) were highlighted among cannabis smokers (53), but the trigger was still unclear. A very severe form of emphysema that is sometimes called "bong lung" is one of the consequences, but little is actually known about this condition.

Pneumonia is another reported complication. Cannabis has been shown to have immunosuppressive effects on alveolar macrophages and to cause loss of ciliated bronchial epithelium (82). Regarding the diagnosis of pneumonia in current users of marijuana within the previous 12 months, some authors found no increased risk compared to non-smokers (83). There are reports of pneu-

monia cases in immunocompromised patients with aspergillosis and *Pseudomonas* (84).

On association with interstitial lung disease are few and occasional reports (one case of eosinophilic pneumonia and a case of pneumoconiosis associated with talc-adulterated marijuana) (75).

Relationship – doses, exposure duration, and diseases

Cannabis use was associated with a greater risk for asthma, COPD and pneumonia, regardless of whether they had a concomitant tobacco-use disorder (85). NHANES study revealed that an association with airflow obstruction ($FEV_1/FVC < 70\%$) was found only in those with over 20 joint-years exposure (51). This was the result of an increase in FVC rather than a disproportional decrease in FEV_1 as it was typically associated with obstructive lung diseases.

More symptoms of chronic bronchitis were described in heavy users (86). Some studies quantified the risk of COPD. Some authors observed a 0.3% increase in the prevalence of COPD for every year of marijuana smoking (87). Even so, a possible explanation for why cannabis is not currently inducing COPD includes a persistent bronchodilator effect (offsetting airway narrowing) or anti-inflammatory or immunomodulatory effects of THC (53).

Quantifying the amount of cannabis when no standardization was implemented was one of the difficulties encountered by researchers in their activity. Compared to tabacco, cannabis daily users consume self-made joints, with different compounds and amounts. One joint-year was defined as 365 joints smoked (53).

Other dangers for cannabis use

Teenagers using e-cigarettes can also become victims of cannabis consumption. Their pathway to cannabis is shorter. In the UK, e-cigarette use by the age of 14 nearly tripled the odds of cannabis initiation by age of 17 (88). More than 100 terpenes and natural extracts, 19 cannabinoids, and other potentially toxic additives such as Vitamin E acetate, polyethylene glycols, and medium chain triglycerides are found in this vaping product and can be produced via vaporizing and aerosolizing the vape oil. Delta-9-THC and potentially toxic additives were found at lower levels in the vapor and aerosol than in the vape liquid (89). Isolated pulmonary Langerhans cell histiocytosis (PLCH) is a rare disease, possibly induced by heavy marijuana smoking, given that tobacco and marijuana contain similar chemical components, and marijuana has a known potential to cause lung diseases with similar features (90). The list is also longer for other reported singular complications like hemoptysis, hypersensitivity pneumonitis, eosinophilic pneumonitis, ARDS, vanishing lung syndrome, aspergillosis, allergic reactions to the weed itself as well as cross reactivity to other allergens such as plant foods in the ''cannabis-fruit/vegetable syndrome (91).

Primary and secondary prevention possible methods

Legalization of consumption seems to be the main prevention method of cannabis induced complications. EVALI incidences were >60% lower in some of the US states where the law allowed home cultivation; similarly, among past-30-day marijuana users, odds of vaping as one's primary mode of use were >40% lower in medical use, only in states where home cultivation was allowed *versus* prohibited (92). Switching to a vaporizer is therefore considered a safer method to use cannabis than smoking (93) – by inhaling only vapors, the consumer is protected from the compounds resulting from the combustion of the mixture and the rolled sheet, especially the tar. Vaporizing must therefore be the preferred delivery mechanism for those patients with chronic respiratory illnesses like asthma and COPD who wish to use cannabis for medicinal purposes. Clearly, due to the potential adverse effects on the developing brain, pregnant women and young adults should avoid cannabis exposure in all of its forms. Cannabis should also be avoided if used combusted or combined with tobacco in a cigarette. Educational campaigns should address potential health risks of cannabis vaping and focus on lung health to reduce use among young people during and following the pandemic (94). ❑

CONCLUSIONS

The effects of smoking cannabis on the lungs are distinct from tobacco, but are not harmless. Larger prospective longitudinal studies are needed, monitoring spirometric changes with the bullous/emphysematous changes on high-resolution computed tomography scans. Reducing or eliminating the benefits of cannabis smoking pa-

tients suffering from symptoms of cough and phlegm is also important. Even though in the last twenty years there has been more evidence in favor of this relation with cannabis regarding emphysema, COPD, infections, and lung cancer, we need more extensive studies for the benefits and impact on lung function. Technological developments should allow researchers to thoroughly exploit all compounds of cannabis, even to discover new ones, and to patent molecular techniques that could improve pharmacological treatment in all conditions. Governments and health care institutes should cooperate in standardizing cannabis usage; otherwise, beyond the harmful behavior under the effect of psychoactive substances, consumption represents a trigger of side effects with an impact on the user's health. Educating young people in order to prevent the initiation in cannabis smoking remains the turning point of future strategies. ❑

Conflicts of interest: none declared.
Financial support: none declared.

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