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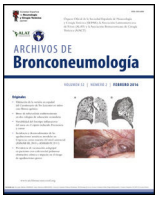

Special article

Lung Disease Associated With Marijuana Use☆

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ABSTRACT

Marijuana is the most widely used illegal drug in the world, with a prevalence of 2.5%–5%, and the second most commonly smoked substance after tobacco. The components of smoke from combustion of marijuana are similar to those produced by the combustion of tobacco, but they differ in terms of psychoactive components and use. Inhalation of cannabis smoke affects the respiratory tract, so the available evidence must be updated in order to provide pulmonologists with the latest scientific information.

In this article, we review the impact of cannabis consumption on the lungs, taking into account that the respiratory route is the most popular route of cannabis consumption.

Patología pulmonar asociada al consumo de marihuana

Palabras clave:
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Marihuana
Hábito de fumar marihuana
Tabaco
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RESUMEN

La marihuana es la droga ilícita más consumida en el mundo con prevalencia de 2,5 a 5% y la segunda sustancia fumada después del tabaco. Los componentes del humo por la combustión de esta sustancia son similares a los producidos en la combustión del tabaco, pero difieren en la sustancia psicoactiva y en la práctica de fumar. La inhalación del humo de cannabis produce consecuencias sobre el aparato respiratorio. Por ello se hace necesario actualizar la evidencia disponible para ofrecer información científica al neumólogo.

En este artículo se revisa el impacto del consumo de cannabis en los pulmones, teniendo en cuenta que la ruta más popular de la ingestión de cannabis es a través de las vías respiratorias.

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Introduction

Cannabis, better known as marijuana, is a dioecious herbaceous plant.[1,2] Marijuana is the name given to the different species of the Cannabis genus, of which *Cannabis sativa* is the most widespread. All species contain terpenophenolic organic compounds called phytocannabinoids. The most well-known cannabinoids are delta-9-tetrahydrocannabinol (THC), cannabinol (CBN), and cannabidiol (CBD). These compounds affect the neurocognitive system by stimulating a series of specific cannabinoid (CB) receptors in the body, the most widely investigated of which are CB1 and CB2.[3–6] The major psychoactive cannabinoid is THC; it has relaxing, analgesic effects but it also causes alteration of the senses, fatigue and appetite stimulation. The next most psychoactive compounds are CBN, a metabolite of THC that has similar effects, and CBD, which has antiepileptic and antiemetic effects, and also affects sleep.[7–10,6]

The aim of this review is to analyze the available literature, focusing on the consequences of regular and continuous use of this substance on the respiratory tract. In this article we will not analyze in depth the political implications of legalization for medicinal or recreational purposes, or other effects on other organs and systems.

Epidemiological Data

Cannabis is currently the most widely used illicit drug worldwide, and is taken by 120–250 million individuals, 2.6%–5.0% of the world's adult population.[11,12] The highest prevalences are reported in North America (10.8%) and Oceania (10.9%), but it is used in most countries.[13] Prevalence data in South America show particularly alarming rates in Uruguay (8.3%) and Brazil (8.8%). The highest rates of use in Central America and the Caribbean are in Bermuda (10.9%), Belize (8.45%), and Barbados (8.3%), although figures are probably significantly underreported.[11]

This drug can be consumed in different forms and via different routes, the most popular being smoking marijuana grass or cannabis resin hashish, but it is also inhaled via vaporizers, ingested or applied to the skin or mucous membranes. Marijuana is consumed by replacing the tobacco in cigarettes or by wrapping it manually in cigarette papers, in pipes, water pipes, or more recently, in vaporizers.[7,14] Marijuana is smoked in longer inhalations than tobacco, the volume inhaled is greater, and the inspiration is held for several seconds. This leads marijuana consumers to retain 3 and 5 times more tar and carbon monoxide, respectively, than amounts inhaled when smoking tobacco.[7] When tobacco and cannabis smoking are compared, it is important to remember that, in addition to the different inhalation techniques described above, tobacco cigarettes are generally smoked more frequently and at shorter intervals, due to the pharmacology of the psychoactive components: the half-life of nicotine is approximately 2 h, while cannabinoids are deposited in fat and can be detected in the body for several days or weeks. Thus, with the exception of time of use, calculations of exposure in terms of amount consumed or accumulated consumption in pack-years for tobacco or number of marijuana cigarettes per year for cannabis cannot be used to estimate the effects on health.[16]

Pharmacological Data

THC is a small lipophilic molecule, rapidly absorbed in the lung: within 4–10 min, it reaches a peak blood concentration[17] that will depend on the THC content of the plant. Psychotropic effects appear in a few seconds or minutes, and last up to 2–3 h. However, bioavailability varies between 2% and 56%, depending on the depth and duration of the inhalation and apnea time.[18]

Except for nicotine and cannabinoids, which occur exclusively in each plant, the components of tobacco and cannabis smoke are similar.[17,19]

Health Effects of Using Marijuana

A study in primates exposed to different doses of marijuana smoke, placebo cigarettes, or common tobacco smoke revealed epithelial hyperplasia in all groups, but a higher incidence and severity of bronchiolitis, alveolar cell hyperplasia with atypia and fibrosis was observed in subjects exposed to marijuana smoke. The authors concluded that endocannabinoids may be responsible for these effects.[20]

For this reason, the damage that marijuana consumption can cause to the respiratory system merits in-depth analysis, not only due to the health implications deriving from the high prevalence of illegal consumption, but because its medicinal and recreational use is now proposed in several countries.[9,11,21]

Most studies have methodological limitations, due in part to the information bias imposed by the consumption of illegal drugs, but also by the limited number of consumers, particularly heavy users, included in the analyses, and the difficulty in quantifying consumption.[1] As marijuana is usually smoked without a filter, the concentration of particles in the airways is 4 times higher than with tobacco smoke. This manner of smoking also generates higher temperatures, modifying biochemical processes and producing many substances.[17] In addition, cannabis and tobacco are often mixed, not only due to overlapping addictions, but also because the mix increases the supply of THC, producing greater psychoactive effects than when cannabis is smoked alone.[3,22,23]

Effects on Lung Function and its Role in Chronic Obstructive Pulmonary Disease

In 1973, some studies described acute bronchodilation in normal subjects and in asthmatics after smoking marijuana with controlled doses of THC in aerosol and orally.[24,25] A suggested mechanism for this phenomenon is stimulation of CB1 receptors in the postganglionic axons of the parasympathetic nerves in the airways, inhibiting the release of acetylcholine and preventing contraction of the bronchial muscles. In contrast, acute exposure to tobacco cigarette smoke is known to induce acute bronchospasm by activation of the cholinergic airway reflexes.[26,27]

In 1997, Tashkin et al.[28] found in a cohort with an 8-year follow-up that, unlike tobacco, smoking marijuana (3 marijuana cigarettes per day) did not accelerate FEV1 decline. However, the authors referred to a low follow-up rate of 65% as one of the limitations of the study.

Ten years later, in 2007, Tetrault et al.[29] reported the acute bronchodilator effects of marijuana use: increased FEV1, peak flow and airway resistance (Raw); and decreased specific airways conductance (sGAW).

In 2012, Pletcher et al.[30] evaluated the association between exposure to marijuana and lung function in a cohort study with a follow-up of more than 20 years. The authors found that in marijuana users, lower exposure was associated with improvements in FEV1 and FVC, but that this effect was lost and FEV1 worsened when exposure was higher, while in tobacco smokers, lung function decline measured by FEV1 and FVC was linearly related with exposure.

More recently, Tashkin[31] confirmed that comparing lung function between marijuana smokers and non-smokers produces heterogeneous results. Some studies found no differences in lung function, others reported a real increase in FVC and/or FEV1, and others reported a decrease in the FEV1/FVC ratio. Macleod et al.,[32]

in a cross-sectional study of 500 cases, found that smokers of marijuana and tobacco showed lower lung function values than smokers of tobacco alone, and that the prevalence of chronic obstructive pulmonary disease (COPD) increased by 0.3% for each marijuana cigarette-year unit.

The few studies that analyzed carbon monoxide diffusing capacity in marijuana users found no significant changes. When airway resistance was evaluated by plethysmography in marijuana smokers, only a modest increase in airway resistance was found, suggesting central airway obstruction.[33]

In the NHANES Nutrition Survey of 2009–2010, data were collected on accumulated use of marijuana. An association was observed between airway obstruction and high consumption but not with mild to moderate consumption, with a cutoff point of 20 marijuana cigarettes-year.[33] Although the mechanism for these findings has not been clarified, a proposed hypothesis is that they are a result of stretching the lungs during the deep and repeated inhalations associated with the usual technique of smoking marijuana.[15]

Aldington et al.,[34] in a study that used chest high-resolution computed tomography, found that marijuana smokers had lower apical lung density than non-smokers and tobacco smokers, but only the latter group showed macroscopic emphysema.

Another study found that the consumption of more than 50 marijuana cigarettes was associated with a higher risk of COPD when smoked in a mixture with tobacco (OR 2.90, 95% CI, 1.53–5.51). The authors found no association between marijuana and COPD, but underline that the power of the study was insufficient to test this hypothesis.[35] Aldington et al.,[34] mentioned above, described an association between tobacco and cannabis consumption and a reduced FEV1/FVC ratio, and although this association was statistically marginal for marijuana, they estimated an exposure/lung effect ratio of 1:2.5–5 between marijuana cigarettes-year in the case of cannabis and pack-years for cigarettes.

In conclusion, results of studies analyzing the association between exposure or use of marijuana and lung function changes are inconclusive. Differences may because most studies included relatively young participants aged <45 years, who are less likely to demonstrate changes in spirometric parameters.

Studies of the effects of marijuana use on respiratory control have been contradictory,[36] but it seems that chronic use does not significantly alter central drive or metabolic rate.[37]

The consumption of marijuana and THC reduces sleep latency, causes sleepiness,[4] increases stage 4 sleep and decreases time of REM sleep, while abstinence is associated with insomnia, reduced slow wave sleep, and REM sleep rebound.[38,39] Similar effects have been observed in neonates of mothers who used marijuana during pregnancy.[40]

Respiratory Symptoms

Most studies indicate an increase in respiratory symptoms, such as cough, dyspnea, sputum, and worsening asthma in habitual marijuana smokers, with or without the concomitant use of tobacco, compared to non-smokers.[4] Marijuana use has also been associated with hoarseness and pharyngitis.[41]

Marijuana users attend emergency departments more frequently with respiratory complaints, particularly exacerbations of bronchial asthma.[29,42]

The NHANES III study[43] reported that smoking marijuana and tobacco increased respiratory symptoms even after adjusting for age, sex, smoking habit, and asthma. The association was maintained for chronic cough (OR=2.00 95% CI 1.32–3.01), chronic expectoration (OR=1.89 95% CI 1.35–2.66), and wheezing (OR=2.98 95% CI 2.05–4.34), but not for dyspnea. One of the most striking observations of this study was that the rates of respiratory symptoms reported by marijuana users were comparable to those of tobacco smokers who were 10 years older, an observation that has been echoed in other studies.[29,31,44–46]

Tashkin et al.[46] followed up a group of tobacco smokers for 10 years, and found a reduction or resolution of respiratory symptoms in participants who gave up marijuana use, while those who continued to use the drug showed a progressive increase in symptoms.

Lung Cancer

The first studies to describe an association between carcinogenic substances and mutagenic changes and marijuana use were published in the 1970s.[47] Polycyclic aromatic hydrocarbons (PAH), such as benzopyrenes and phenols, are produced in marijuana smoke, suggesting that the consumption of marijuana may also be a risk factor for cancer, particularly of the lung.

Squamous metaplasia and tumor progression markers have been observed in bronchial biopsies of marijuana smokers, and changes in the expression of genes involved in the development of cancer were observed in experimental animal models.[48]

Epidemiological studies that attempt to measure the association between marijuana and cancer have limitations. The main methodological drawbacks of these studies are that marijuana smokers are usually also concomitant tobacco users, sample sizes are generally small, participants are young, and data are biased, as marijuana is an illicit drug.[49] These factors might, at least in part, explain the contradictory results from the various studies.

An analysis investigating the marijuana use and its association with head and neck cancer found an OR of 2.6, 95% CI 1.1–6.6, but other studies did not obtain these results.[50,51]

In California, a retrospective cohort study of 64,855 individuals aged 15–49 years examined the association of self-reported marijuana use with cases of cancer over a mean follow-up of 8.6 years. Marijuana use was not associated with an increased risk of cancer, after adjusting for tobacco and alcohol consumption, socioeconomic level, and sex. An important limitation of this study is that participants were young and the follow-up period was relatively short. Thus, during the observation period, most of the cohort had not yet reached the age at which the incidence of cancer is relevant.[51]

In 2006, Mehra et al.[52] published a similar review in which they found no association between marijuana smoking and lung cancer, but the authors point out the same limitations mentioned above. In 2008, Berthiller et al.[53] reported an association between cannabis use, describing 430 cases of lung cancer compared to 778 controls in a case control study. The results remained statistically significant after adjustment for the consumption of tobacco in pack-years, OR=2.3, 95% CI: 1.5–3.6. In 2013, Callaghan et al.[54] questioned 49,321 men about their consumption of tobacco and marijuana during their military service when they were aged 18–20 years old. The cohort was followed for a further 40 years. They found a positive association between lung cancer and marijuana smoking when lifetime consumption was greater than 50 marijuana cigarettes, with a 2-fold increase in risk (HR 2.12, 95% CI 1.08–4.14) even after adjustment for tobacco and alcohol use, other respiratory diseases, and socioeconomic status.

To overcome methodological difficulties, in 2015 the International Lung Cancer Consortium[49] investigated the association of marijuana smoking and lung cancer in 2159 cases and 2985 controls in pooled data from 6 studies. The results were inconclusive, but a higher risk was observed in cannabis user than in individuals who had never smoked tobacco.

Nevertheless, another case control study examined 1212 cases of cancer, 611 of which were lung cancer, and 1040 control cases

with a comprehensive history of drug, tobacco and alcohol use, occupational exposure, diet, and family history of cancer over a 5-year period. Results showed an association that was lost in the adjusted analysis. The authors acknowledged limitations in this study, but concluded that the association between marijuana and lung cancer is not strong.[50]

In conclusion, available evidence suggests that the use of marijuana at high doses, and perhaps moderate doses, may be a risk factor for lung cancer, a hypothesis that appears to be plausible.[48,55] A recent systematic review reached similar conclusions.[56]

Bullous Disease, Pneumothorax and Pneumomediastinum, Barotrauma

Cases have been reported of bullous disease,[57,58] emphysema,[59] pneumothorax, and pneumomediastinum[60] associated with the use of marijuana in young patients.[44,57,61–63] However, as these studies are generally only case series, no association or causal relationship could be established.[44]

Marijuana smoking techniques might explain these events.[60–63] "Shotgunning", exhaling smoke into the mouth of another person, is another practice that could be related with these cases.[64] Lastly, some authors suggest the existence of inflammatory mechanisms in the bullae of marijuana smokers.[65]

Risks of Respiratory Infection

Marijuana smoke damages the epithelium, with loss of ciliated cells and hyperplasia of mucus-secreting goblet cells. These changes cause reduced mucociliary clearance, with mucus accumulation and bacterial colonization increasing the risk of infections in the respiratory tract.[66] THC also alters the bactericidal and fungicidal activity of the alveolar macrophages.[3]

Cannabinoids affect the functioning of immune cells, such as B and T lymphocytes and NK cells,[27,67] and can also alter the expression of many cytokines.

Marijuana contaminated with *Aspergillus fumigatus*[68] and Gram-negative bacteria[69] has also been encountered, possibly explaining some very severe cases of aspergillosis in marijuana smokers with immune deficiency due to HIV-AIDS, chronic granulomatous disease, bone marrow transplant, kidney transplant and cancer treated with chemotherapy.[70,71]

The spread of tuberculosis by sharing marijuana cigarettes or water pipes has also been described.[72,73]

Marijuana is an independent risk factor for opportunistic lung infections in HIV-Aids. However, neither marijuana nor other psychoactive drugs were identified as a risk factor for accelerating immunodeficiency in a multicenter cohort study.[74]

Legalization of Marijuana use and Public heAlth Risks

Without going into the possible political and strategic considerations for the control of drug trafficking, the legalization of cannabis for recreational use can be expected to contribute to an increase in social tolerance and a normalization of consumption.[1,4,9,10,75] This drug will not only be more accessible, but also more affordable for the entire population.[76]

To date, the available studies and observations on the effects of policies legalizing the use of marijuana do not provide sufficient evidence to judge the benefit and/or harm of such actions. Very few countries have agreed to implemented such policies, so this would be a good moment to propose global strategies for the control of these substances, similar to the FCTC[77] and MPOWER.[78]

Conclusions

Evidence shows that active inhalation of marijuana smoke is associated with respiratory diseases and in particular with COPD and cancer when smoked concomitantly with tobacco. The composition of marijuana smoke is similar to that of tobacco smoke, so the increasing consumption of cannabis by inhalation in the last few decades should alert the scientific community to the possible impact on lung health.[79–85]

The available evidence is still inconclusive, and many aspects need confirmation or further studies. However, in their daily practice, physicians, and in particular respiratory medicine experts must address the use of marijuana, especially among young people. Individuals must be informed that the recreational use of this substance is not free of risks to health in general and the respiratory tract in particular.[6] The available evidence tends to be limited by imprecise methods of determining exposure to marijuana smoke and recording data, and by the fact that in most countries consumption is still illegal, impeding the collection of accurate information.[86] We need new studies that carefully take into account these shortcomings, as well as more basic research in animal models exploring the effects of marijuana on the respiratory tract.

While the medicinal use of cannabis derivatives with proven scientific evidence and products currently under development is acceptable, the usual procedures for the evaluation of any drug must be followed, and recreational uses must be considered separately.

Conflict of Interests

The authors state that they have no conflict of interests.

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