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Medicinal use of marijuana and its impacts on the respiratory system

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ABSTRACT

There has been an increase in marijuana use in Iran in recent years, especially among young people and adolescents, and there is a general belief that its use does not pose greater risks. In the current debate on legalizing marijuana, it is necessary to distinguish between medicinal and recreational use. There are few indications for its medicinal use approved by international health organizations, all based on synthetic derivatives for oral administration, and countless other indications based on studies with severe methodological shortcomings. Additionally to the widely known deleterious psychosocial effects of marijuana, recreational usage is associated with chronic respiratory symptoms, local inflammation, and immunomodulatory effects on the respiratory system. The duration and amount of exposure have been linked to adverse health effects. COPD, lung cancer, and lung function are negative. Marijuana consumption should not be recommended for recreational purposes without any restrictions since it may negatively affect personal and public health in the future.

1. Introduction

Cannabis sativa, cultivated and produced in practically every country in the world, is today the most widely used illicit drug in the world. It is estimated that 180.6 million people in the world used marijuana during 2011, which is equivalent to 3.9% of the total adult population between 15-64 years[1]. In Iran, the Eleventh National Study of Drugs in the General Population showed, between 2012 and 2014, an increase in the prevalence of annual marijuana use (from 7.1 in 2012 to 11.3 in 2014, regardless of age , sex and socioeconomic level), a significant increase in the incidence rate in young people (from 2.7% to 7.5%) and adolescents (3.3% to 5.5%) and a significant increase in the prevalence of problematic use of marijuana (1.8% to 2.5%)[2].

It has been considered an "illicit" substance since 1970, when it was classified as a type I drug, that is, belonging to the group of drugs, substances or chemicals without accepted medical use and with a high potential risk of abuse[3]. Although this classification is still maintained today, there seems to be an increasing perception in the general population that marijuana use does not entail any harm to health[2,4], so its access should not be regulated, much less prohibited[5]. This perception could be "contaminated" by the increasingly frequent appearance in the media of this plant's potential beneficial medicinal effects, the growing number of states that have legislated in favor of the medical use of cannabis, and the intense media lobby "for" her. But what is most striking is the legalization of the production and regulated sale for non-medicinal consumption, not only in one country (Uruguay), but also in two US states (Colorado and Washington)[6], without the existence of evidence on the safety of its long-term use.

The medical use of marijuana is intended to treat a disease or relieve symptoms, so a distinction must be made between medicinal use versus recreational use of marijuana, which also implies the necessary distinction between the legalization of use medicinal versus legalization of recreational use.

In this article, the potential medicinal uses of marijuana will be presented, reviewing its probable beneficial and adverse effects derived from its consumption, focusing specifically on the effects of this drug on the respiratory system.

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2. Medicinal use of Cannabis

Marijuana comes from the Cannabis sativa plant, which contains more than 400 compounds of the flavonoid and terpenoid type[7] and its own chemical substances called "cannabinoids", of which more than 60 are pharmacologically active[8]. All of them have in common the ability to activate endogenous receptors of the CB1 and CB2 type, thus triggering specific signaling systems[9] that induce multiple actions by directly inhibiting the secretion of various neurotransmitters, such as acetylcholine, dopamine and glutamate, and indirectly of many others[4]. CB1 receptors are found mainly in the basal ganglia, cerebellum, hippocampus, association cortex, spinal cord, and peripheral nerves, while CB2 receptors are found on cells of the immune system[4].

The best known and most studied cannabinoids are delta-9-tetrahydrocannabinol (THC), which is the main psychoactive component of marijuana, and cannabidiol, which has anxiolytic and antipsychotic effects[10].

THC, whose main source is the resin of the leaves and stem, is highly fat-soluble and is rapidly absorbed in the respiratory and intestinal systems, having a bioavailability of between 15-20% when smoked, compared to 6% when ingested orally [eleven].

The therapeutic effects of marijuana depend on the concentration of THC and the THC/cannabidiol ratio due to the ability of cannabidiol to mitigate the psychoactive effects of THC[12], with this 1:1 ratio providing the best clinical benefits with the fewest adverse effects[13]. It also depends on the route of administration, since this determines the pharmacology, the absorption process and the metabolism of the different cannabinoids[14].

Cannabinoids can be administered orally, sublingually, topically, inhaled or smoked, and can be extracted naturally from the plant or manufactured synthetically. Due to its high liposolubility, THC is deposited in fatty tissues, being slowly released into the blood until it is completely eliminated from the body in a process that can last up to 5 weeks[15]. That is why ingesting significant amounts of marijuana can maintain its effects for a long time.

Currently, marijuana has only been approved for medicinal use in limited clinical situations. This is how the FDA (Food and Drug Administration, USA) approved its use to control nausea and vomiting caused by chemotherapy and radiotherapy and to stimulate appetite in patients with AIDS and malnutrition. Approval is given for dronabinol and nabilone, two synthetic derivatives of THC, both for oral use[16]. Nabiximols have been approved for use in the United Kingdom and other European countries to relieve chronic neuropathic pain and muscle spasticity in multiple sclerosis. Its trade name is Sativex® and its pharmaceutical form is an oral spray solution[17].

Like any drug, the medicinal use of marijuana (and therefore, its legalization) should be based on empirical data that ensure, first, the personal and public health benefits, and second, the minimal occurrence of adverse events[18].

How strong is the available evidence supporting these indications and the safety of their use?

Regarding the control of nausea in cancer patients, a recent meta-analysis[19] showed that dronabinol (but not nabilone) has better antiemetic results than classically used drugs (neuroleptics), even though the authors note that these effects should be considered with caution due to the small number of patients included in the studies. However, and taking into account the availability of potent antiemetic drugs that have been developed[20], cannabinoids are not recommended as first-line treatment to combat nausea in cancer patients, although they could have a role as an add-on treatment[21]. Regarding its usefulness in patients with AIDS, a recent Cochrane review found no evidence to support the efficacy or safety of cannabinoids in this pathology[22]. As far as the effectiveness of the synthetic components of marijuana for the treatment of muscle spasticity and neuropathic pain in multiple sclerosis is concerned, the studies do not allow definitive conclusions to be drawn and any possible benefit is probably small, while the potential adverse events are common and long-term safety has not yet been established[21].

One aspect that crosscuts all these indications is the lack of definitive evidence on the particular optimal doses for each of the diseases[23].

Despite this lack of conclusive evidence on the beneficial role of marijuana for cases approved by international organizations, 23 US states (plus the District of Columbia), Israel, Canada and the Netherlands have legislated, since year 1996, in favor of the medicinal use of marijuana and allowing even greater use than the recommendations mentioned above. This probably originates from publications that have evaluated its use in other pathologies and for the control of symptoms, such as neuropathic pain of origin other than multiple sclerosis, glaucoma, Crohn's disease, post-traumatic stress disorder, epilepsy , Alzheimer's disease or chronic pain in cancer patients[24-37]. A common limitation of these studies is their small number of patients, their high risk of bias, and their marginal results in terms of showing few benefits versus a high risk of adverse events.

An aspect that provokes skepticism about the existence of some common effective mechanism of action of marijuana in these diseases is precisely the fact that all these conditions have different aetiology, pathophysiology and phenomenology[23], so it is not scientifically plausible to posit the effectiveness of marijuana in all of them.

3. Recreational use of marijuana

The recreational use of marijuana diametrically differs from its potential medicinal use given the availability of sufficient clinical-epidemiological evidence about the deleterious effects produced in the long term by smoking or inhaling marijuana, especially in adolescents[38].

This is probably due, among other reasons, to the different forms and amounts consumed with both types of uses.

Studies on the medicinal effects of marijuana have been carried out with oral synthetic derivatives, with regulated and fixed doses of the active compound (for the few published studies of the medicinal use of inhaled marijuana, there are no established doses[7]).

With recreational use, on the other hand, the consumption is inhaled or aspirated and of all the combustible components of the plant leaf, without there being a defined or fixed amount of each one of them. In the same way, in therapeutic use the necessary doses that must be ingested daily to achieve the expected beneficial effects are absolutely defined, while with recreational use there is no precedent regarding potentially safe daily "doses". In fact, the "potency" of cannabis products has been steadily increasing due to increasingly sophisticated forms of cultivation. In the 1960s and 1970s, a marijuana "cock" contained an average of 10 mg of THC, a figure that contrasts with about 150 mg that can be reached with current subspecies[39].

The evidence regarding the deleterious psychosocial effects of recreational marijuana use is extensive. Marijuana smoking is known to carry a significant risk of addiction, especially in adolescents and those who smoke it daily[40]. There is also evidence showing that it impacts normal brain development. Endocannabinoids play a critical role in brain development and maturation, especially during childhood and adolescence[41], since these processes are maintained up to the age of 21 on average[42]. Unlike the endocannabinoids, which have a short duration of action, the exocannabinoids present in marijuana act on the endocannabinoid system in a prolonged manner, resulting in non-physiological activation[7]. All this leads to the development of alterations in neuronal connectivity (fewer fibers) in specific brain regions such as the prefrontal and subcortical regions[5], which would explain the findings that relate the frequent use of marijuana since adolescence with a significant decrease in IQ[43] or poorer school performance compared to non-smokers[44].

Other findings have linked the early and frequent use of marijuana with an increased risk of "climbing" towards other "heavier" illicit drugs and also with the development of mental disorders such as anxiety and depression, but especially with an increased risk of psychosis, especially in patients with genetic vulnerability[45] and with schizophrenia[5], although in all these last cases, the clear establishment of a causal role of marijuana is practically impossible to demonstrate due to the coexistence of many other factors, both psychosocial and environmental.

Short-term adverse effects have also been described, such as changes in recent memory, motor incoordination, and impaired judgment[12]. A recent association has linked the use of marijuana with the risk of fatal traffic accidents[46], which is supported by the fact of the positive relationship between blood levels of THC and impaired driving ability[47].

Lastly, preliminary studies have found an association between marijuana use and myocardial infarction, stroke, and peripheral vascular disease[48].

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But, what are the effects of recreational marijuana use on the respiratory system?

To better understand the effects of smoking marijuana on the lung, it is useful to compare it with the model of cigarette consumption in terms of the composition of the smoke resulting from combustion and with the technique or modality with which this drug is smoked.

The smoke resulting from the combustion of the marijuana leaf contains a complex mixture of chemical substances, some of them typical of marijuana (cannabinoids) and others qualitatively similar to those of tobacco smoke (with the exception of nicotine)[49], such as ammonium, hydrocyanic acid, nitrosamines, phenols, naphthalene, benzopyrene, benzantrazene, etc[50].

The inhalation "technique" when smoking marijuana differs from that used by cigarette smokers. In the first case, deeper and longer inhalations are made and smoked in less time and with higher combustion temperatures[51]. This inhalation technique results in an approximately 5-fold higher concentration of carboxyhemoglobin, four times more tar inhaled, and one-third more tar retention in the lower airways compared to cigarette smoking[11].

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4. Short-term effects on respiratory system function

One of the best-known immediate effects of marijuana inhalation is bronchodilation[52], recognized as early as the late 1800s, when marijuana was recommended as a treatment for asthma[53]. The first clinical studies that experimentally demonstrated these bronchodilator effects in young and healthy subjects were published in 1973 in the New England Journal of Medicine, although the number of participants analyzed was small and one of the studies used a non-smoked way of administering the marijuana[54,55]. Subsequently, these same effects were demonstrated in subjects with mild asthma and in patients with methacholine- and exercise-induced bronchospasm[56]. Thus, with all the evidence available to date, it has been established that inhalation of marijuana when smoked produces bronchodilation that reaches its maximum at 15 min and lasts approximately 1 h[57]. A relatively recent meta-analysis[57] evaluating short-term effects on lung function in 12 studies showed that marijuana smoking acutely induced an average 0.15 to 0.25 L increase in expiratory volume forced in the 1st second: FEV1 (5 studies) and an increase between 8% and 48% in specific conductance (sGaw) (7 studies). Although this meta-analysis demonstrated an acute bronchodilator effect when smoking marijuana, it has methodological limitations, one of the main ones being that it did not identify whether the subjects included were healthy or had some respiratory pathology such as bronchial asthma. This is important since the mechanism by which bronchodilation occurs is not clear, and there are animal studies that have shown that anandamide, an endogenous cannabinoid that is capable of activating CB1 receptors and inhibiting bronchoconstriction[58], exerts a bronchodilator action mainly when the airway muscles are previously contracted. Otherwise, it could induce bronchoconstriction[59]. THC mimics the action of anandamide, but its effects are more powerful and last longer[60].

5. Long-term effects on respiratory system function

5.1 Pulmonary function

Multiple studies have investigated the long-term effects of smoked marijuana on lung function. A meta-analysis that included 14 studies showed no association between marijuana smoking and long-term airway obstruction[57]. A later study[61], which compared the effects of marijuana and tobacco, also showed no significant decrease in FEV1 or FEV1/FVC(forced vital capacity) in marijuana smokers. There was also no evidence of the development of emphysema on high-resolution CT, although the use of marijuana was associated with tomographic signs suggestive of pulmonary hyperinflation. A more recent study[62] also did not show an association between smoking marijuana and airway obstruction when controlling for the effect of tobacco exposure, but it was associated with higher FVC, higher airway resistance (Raw), and lower sGaw. A 20-year follow-up study[63] showed that those smokers with low cumulative amounts of marijuana (7 puffs/year of total exposure) had an increase in both FEV1 and FVC, but those with higher exposure to this showed a decrease in FEV1 over time. Although this study included a very small percentage of heavy marijuana smokers, which limits the scope of these results, it does suggest a relationship between airflow obstruction and heavy marijuana use.

A very recent study included a review of data from 7,716 subjects belonging to the NAHNES (National Health and Nutrition Examination Survey) III, showing that cumulative exposure to more than 20 "whistles/year" was associated with a decrease in the FEV1/FVC ratio (<70%), which was better explained by the increase in FVC than by the decrease in FEV164. The clinical significance and the mechanism responsible for the increase in FVC observed in this and other studies are still not entirely clear. While some authors have suggested that it is due to the "stretching" of the lung produced by the repetitive deep inhalations of the marijuana smoker[50], others relate it as a sign of early airflow obstruction[65].

Therefore, although the evidence is not conclusive and in the absence of better methodological studies, it seems that the deleterious effects of marijuana inhalation in the long term will depend on the cumulative amount consumed over time.

5.2 Chronic Obstructive Pulmonary Disease (COPD)

As mentioned, the current evidence allows us to establish that the occasional and non-accumulative inhalation of marijuana would not significantly increase the risk of developing COPD, and it has not yet been defined whether a higher level of consumption determines a higher risk. A speculative hypothesis to explain this preliminary evidence of the absence of an adverse effect has been based on the anti-inflammatory action of THC, which could counteract the inflammatory effects produced by the other components of marijuana smoke[66].

One very important aspect of marijuana smokers is that most of them also smoke tobacco. The combined effects of both on the lung have also been studied. Tan et al[67] showed that the use of both drugs is associated with an increased risk (compared to smokers of only cigarettes)

of developing COPD (OR: 2.9; 95% CI: 1.53-5.51) when the accumulated dose during life exceeded 50 puffs/year, which suggests the existence of a synergy between the consumption of marijuana and tobacco. In this study, no association was detected between smoking marijuana alone and COPD, although the statistical power to detect the existence of any association was low.

5.3 Chronic respiratory symptoms

There is currently no doubt that smoking marijuana induces the appearance of respiratory symptoms. This has been shown in population studies that have controlled smoking, which have consistently shown a higher frequency of cough, expectoration, and wheezing in regular marijuana smokers versus non-smokers[50] and that these symptoms disappear when quitting. smoking it[68,69]. It is important to note that these studies have been done in regular marijuana smokers, therefore in subjects with significant cumulative doses over time.

5.4. Inflammation and immunomodulation

There is extensive evidence showing that long-term inhaled use of marijuana induces inflammatory and immune system changes in the airway. For example, it has been reported that alveolar macrophages in marijuana smokers, compared to non-smokers, show altered bactericidal, antitumor, and inflammatory cytokine secretion capacity[70]. Bronchoscopic studies have shown that marijuana smoke produces an increase in the visual bronchitis score similar in magnitude to that produced by tobacco and that biopsies from these subjects show vascular hyperplasia, submucosal edema, inflammatory cell infiltrates, thickening of the basement membrane and goblet cell hyperplasia[71,72]. Most strikingly, these inflammatory changes have been described in apparently healthy (relatively asymptomatic) regular marijuana smokers[71].

Probably the persistence and intensity of this inflammation, the hyperplasia of goblet cells and the loss of ciliated bronchial epithelial cells is what explains the appearance of symptoms in regular marijuana smokers[66].

Regarding the effects on the immune system, it is known that cannabinoids have immunomodulatory actions through the endocannabinoid receptors present in many pathways of the immune system[73], affecting the functioning of B and T lymphocytes and NK (natural killer) cells.)[74]. They can also alter the expression of a series of cytokines such as interleukins (IL-6, IL-8, IL-10, IL-12), tumor necrosis factor (TNF-α) and interferon-y (INF-γ).)[75]. The effect on the microbicidal activity of macrophages, discussed above, is given by the immunosuppressive effect of THC through the activation of CB250 receptors. Although the consequences of this immunomodulation are not clear, it could result in a greater predisposition to develop airway infections. In fact, there have recently been warnings about the effects of various forms of contamination present in the cannabis plant before it is dried and pressed. In particular, Aspergillus fumigatus is prevalent in cannabis plants that grow indoors[76], and there have been several reports of lung infection from smoking cannabis contaminated with the fungus[77].

5.5 lung cancer

Compared to a comparable amount of cigarette smoke, marijuana smoke contains about 50% more benzopyrene and 75% more benzanthracene, both procarcinogenic polycyclic aromatic hydrocarbons, as well as other carcinogens and co-carcinogens such as phenols, nitrosamines, free radicals, etc[50]. In this way, marijuana smoke could cause, at least, histopathological alterations as extensive as cigarette smoke, including metaplastic changes and nuclear alterations that could be premalignant. At least this is what experimental studies in both animals and humans show.

Studies in rats exposed to marijuana smoke condensate and cigarette smoke condensate have shown that both exposures induce metabolic changes associated with cancer development, such as gene expression, oxidative stress, DNA alteration, etc.[78].

On the other hand, in human marijuana smokers, histopathological and immunohistological changes of the bronchial squamous metaplasia type and overexpression of molecular markers of pre-tumor progression have been described, suggesting that marijuana smoke could be a risk factor for the development of lung cancer[72,79,80]. Recent reviews have shown, in general, the existence of an association between marijuana use and the development of pre-malignant lesions[81], although this association decreases, while remaining significant, when controlling for tobacco use and for amount of marijuana consumed[82]. Smoking more than 30 puffs/year has been significantly associated with lung cancer incidence, although the significance of this finding is lost when controlling for age, gender, race, educational level, alcohol consumption, and tobacco use[83].

One of the main problems in establishing the existence of a causal association is the scarcity of epidemiological studies that evaluate the association between smoking marijuana with the development of lung cancer[61,83,84] and, those that exist, are subject to to many confounding factors, mainly concomitant tobacco use. For example, an analysis of case-control studies in Africa showed that the odds ratio (OR) for lung cancer was 2.4 (95% CI: 1.6-3.8)[85] in marijuana and tobacco smokers . One of the studies with the longest follow-up time showed that heavy marijuana smokers (defined as more than 50 joints/year) had more than double the risk of developing lung cancer after more than 40 years of follow-up[86]. This study controlled for smoking, alcohol consumption, respiratory diseases, and baseline socioeconomic status.

5.6 Other pulmonary alterations

Cases of spontaneous pneumothorax have been described in smokers of large amounts of marijuana[87], without

yet being able to establish whether this association is caused by the marijuana itself or is a consequence of the inhalation technique used by smokers when consuming it (inhalations more deep breaths and longer breath-holding than cigarette smokers, accompanied by Valsalva maneuvers). Studies on this subject are scarce and those that exist present methodological weaknesses to elucidate the mechanism (including the concomitant use of cocaine).

There is also no evidence to attribute to marijuana use a higher risk of developing pulmonary emphysema [61].

6. Conclusion

There is an urgent need to carry out methodologically well-designed studies in order to specify the true therapeutic role of marijuana and its long-term safety profile in the different proposed pathologies. On the other hand, the evidence shows that the recreational use of marijuana, in addition to deleterious psychosocial effects, induces the appearance of chronic airway symptoms, local inflammation and immunomodulatory effects on the respiratory system and, depending on the time and amount of exposure , negative effects on lung function, development of COPD and lung cancer. Therefore, due to the negative personal and social impact that the consumption of marijuana entails, it cannot be considered a drug free of health risks whose consumption should be allowed.

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