Editorial

Use of Medical Cannabis for Respiratory Diseases

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Cannabis is a genus of flowering plant within the Cannabaceae family. For thousands of years, the plant has been cultivated and used worldwide for a variety of purposes; in small industries, in agriculture and livestock farming, as a recreational drug as well as in medicine[1].

Currently, there is no consensus regarding its classification within the Cannabis genus[2]; some researchers have proposed a differentiation of at least two species – Cannabis Sativa and Cannabis Indica. Other taxonomists have suggested that the unique species Cannabis Sativa exists and the subtypes of this plant vary depending on the different proportions of cannabinoids and terpenoids that the plant may contain.

At least 750 chemical substances were isolated from the cannabis plant, 104 of which are identified as cannabinoids (also known as phytocannabinoids). The most significant cannabinoids in relation to health effects are: Δ^9–tetrahydrocannabinol (THC) and cannabidiol (CBD)[3].

The cannabinoids affect the function of the **endocannabinoid system**, which has three components: CB1 and CB2 cannabinoid receptors, endogenous endocannabinoids produced in the organism and enzymes that regulate endocannabinoid synthesis and metabolism[4].

THC is a partial agonist of CB1 and CB2 receptors. The CB1 receptors are primarily found in the central nervous system (brain and spinal cord), in the areas that regulate cognitive function, memory and emotions, appetite and nausea, pain and motor responses. The fact that it is located in the CNS explains the psychoactive effects of THC[3]. It should be noted that CB receptors are not located in the respiratory center and do not directly affect the act of respiration[5]. Also, CB1 receptors are present in the peripheral nervous system, the gastrointestinal tract, liver and skeletal muscles. CB2 receptors, in contrast, are situated primarily in tissue macrophages and other immune cells, and are responsible for the immunomodulatory and anti-inflammatory effects of cannabis.

CBD has low affinity to CB1 and CB2 receptors and lacks psychoactivity. CBD affects other receptors by utilizing many other mechanisms, modulating the activation of various enzymes and has potential analgesic, powerful anti-inflammatory, anticonvulsant, anti-psychotic and anxiolytic properties[3].

Both cannabinoids mentioned above are believed to possess antioxidant effects.

The medical use of cannabis has a long history that dates back at least 2 thousand years. Interest in the therapeutic qualities of the plant has been growing over the last 20 years, substantiated by the dozens of randomized studies that have been conducted with thousands of participants. More data is being collected towards gaining a better understanding of the biological activity of synthetic cannabinoids, their medical indications, modes of administration and side effects.

There are currently a number of FDA approved **synthetic cannabinoids** available: Dronabinol and Nabilone (synthetic Δ9–THC prescribed for cancer patients with chemotherapy-induced nausea and vomiting and for treating anorexia and weight loss in AIDS patients). Other cannabinoid-based medications have been examined by the FDA and are expected to be licensed for medical use (Ajulemic acid could potentially be prescribed to relieve spasticity associated with multiple sclerosis).

The most common conditions for which the medical use of cannabis and cannabinoids has been thoroughly researched are: chronic pain including neuralgia and cancer-induced pain, nausea and vomiting associated with chemotherapy, anorexia and weight loss in patients with AIDS, irritable bowel syndrome, epilepsy, muscle spasticity in patients with MS, Tourette's syndrome, Huntington's disease, glaucoma, anxiety, sleep disorders and various psychoses[6].

Synthetic cannabinoids, (synthetic Δ9–THC) Nabilone and Dronabinol, have been used legally since 1985 as an antiemetic treatment for cancer patients undergoing chemotherapy. Recently, investigators have proven that Dronabinol is as effective as Ondasetron in these cases.

Also, in the treatment of cancer patients, cannabis is used for its cannabinoid-induced analgesic effect as well as its anti-inflammatory properties. In lung cancer patients with breathlessness and strong opioid-resistant pain, it can be used as an anxiolytic and analgesic treatment[5].

It is an interesting fact that chronic use of synthetic cannabinoids usually does not require a gradual increase in dosage, in contrast to opioid-based treatments[7].

Although sporadic cases of respiratory depression with symptoms of acute respiratory failure and respiratory acidosis have been reported in patients receiving synthetic cannabinoids, it cannot be clearly ascertained whether these effects are due to the use of cannabis since it has not been adequately studied. It is speculated to be related to CB1 receptor stimulation, without specifying whether it was the result of an overdose of cannabinoids or whether it was a synergistic effect of other drugs[8].

Association between cannabis smoking and pulmonary function, possible beneficial and adverse effects on the respiratory system, has been studied by researchers over the last 20 years.

Tetrault et al. found that short-term exposure to cannabis smoking is associated with improvements in FEV1, FVC, peak flow measurements, and reversal of provoked bronchospasms resulting in bronchodilation[9]. Subsequently, in vitro trials conducted by researchers Grassin-Delyle et al. attributed this effect to the inhibition of cholinergic contraction in human airways through the activation of prejunctional CB1 receptors[10]. However, a number of studies revealed that regular cannabis smoking may result in adverse effects on the human bronchus owing to the combustion of the compounds in cannabis at high temperatures, which produces toxic byproducts. On the contrary, cannabis vaporization is linked to milder pulmonary symptoms compared to smoking[11].

In 2011, Pickering et al. investigated the impact of Sativex (THC: CBD=1:1), in spray form, on pulmonary ventilation and breathlessness in COPD patients. The results did not show any improvements in conventional breathlessness ratings and ventilatory parameters. Yet, COPD patients reported fewer instances of feeling of dyspnea[12].

An ongoing, large-scale clinical trial currently being conducted in the U.S. is looking into the effects of Dronabinol on patients with obstructive sleep apnea (OSA). The Phase II results are encouraging. The authors report: "in comparison to the placebo, Dronabinol was associated with a lower apnea/hypopnea index, improved subjective sleepiness, and greater overall treatment satisfaction"[13]. Nonetheless, the position of the American Academy of Sleep Medicine is that medical cannabis should not be used for the treatment of obstructive sleep apnea, and OSA "should be excluded from the list of chronic medical conditions for state medical cannabis programs... until there is scientific evidence of safety and efficacy"[14].

There are reports of administration of medical marijuana that have no substantial evidence to support the use of cannabis or cannabinoids as a treatment for other respiratory diseases. Cannabis, acting as anti-inflammatory[15], bronchodilatory[10] and antibacterial agent, may reduce COPD exacerbations, while immunomodulatory properties[16] probably slow the progression of chronic bronchial constriction and emphysema. The anti-inflammatory effect of CBD has been studied for the treatment of inflammatory lung diseases, such as acute lung injury and acute respiratory distress syndrome[17].

It should be noted that the medical use of cannabis is complicated due to the chemical constituents of the plant as well as its pharmacokinetic and pharmacodynamic interaction in the organism.

Other chemical compounds of cannabis, including flavonoids, terpenoids, vitamins, amino acids, proteins, glycoproteins, steroids, nitrogenous compounds and enzymes may modulate each other in synergistic or antagonistic ways. This behavior reveals the need for further studies focusing on the interaction between these components.

Therapeutic benefits and side effects of the treatment vary depending on factors such as: the chemical variations of the plant as a raw material, the form of cannabis product used (fresh, dried, heated) and the mode of administration (smoking, vaporizing, oral or topical use)[6].

THC absorption and metabolism differ among the general population and thus individualization of the dosage is required with a low starting dose and slow titration, targeting the lowest effective dose in order to avoid undesirable effects[3,6].

Different types of diseases necessitate particular combinations of active ingredients such as varying proportions of THC and CBD.

ADVERSE EFFECTS

The most common unfavorable effects of cannabis-based medications are related to THC; drowsiness, euphoria, dizziness, ataxia, depression, anxiety, headaches, hallucinations, psychosis and nausea. In addition, dry mouth, tachycardia, orthostatic hypotension and diarrhea are commonly reported. The adverse THC-induced effects are dose-dependent and can be reduced by dose titration and/or the use of a combination of CBD-predominant medications[3,6].

Regular marijuana cigarette smoking is associated with productive cough, reversible by quitting cannabis smoking. Nevertheless, according to studies, COPD development, a range of COPD or asthma exacerbations and the risk of lung cancer in regular marijuana smokers are not supported by significant evidence and are related mostly to mixed marijuana and tobacco smoking.

The medical use of cannabis is contraindicated in pregnancy and lactation as well as in patients with severe mental disorders (THC-based medications), while in patients with cardiovascular diseases, the use of cannabis products should be administered with caution.

CONCLUSIONS

In conclusion, cannabis and synthetic cannabinoids are widely used in medicine for multiple therapeutic purposes. A number of synthetic cannabinoids have been approved for treating chemotherapy-induced nausea and vomiting. Moreover, medical cannabis has been used for its analgesic and anxiolytic effects in lung cancer patients with breathlessness. It can also be administered to COPD patients since marijuana has a bronchodilator effect and reduces the unpleasantness of dyspnea. The anti-inflammatory property of CBD has been studied for the treatment of inflammatory lung diseases, such as acute lung injury and ARDS.

Though cannabis has a sedative effect and provokes daytime sleepiness, it should be noted that CB receptors are not located in the respiratory center and do not directly affect the act of respiration. There is weak evidence connecting smoking marijuana to the development of COPD, asthma exacerbation or risk of lung cancer.

Clinical trials provide a broader understanding of the biological effects of cannabis, its mode of administration and treatment dose titration. More data regarding new indications for medical use is expected. Yet, further research is needed; better designed long-term studies intended to elucidate its safety and adverse effects on the respiratory system are required.

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