

Medical Cannabis in Asthmatic Patients

Amir Jarjou'i MD and Gabriel Izbicki MD

Pulmonary Institute, Shaare Zedek Medical Center, affiliated with the Hadassah–Hebrew University School of Medicine, Jerusalem, Israel.

ABSTRACT: **Background:** With the increased use of cannabis in the medicinal and recreational domains, it is becoming more important for physicians to better understand its harmful and beneficial effects. Although medical cannabis comes in several forms, the preferred route of administration is smoking or inhalation. After caring for three asthmatic patients who were treated with medical cannabis and who reported improvement in their symptoms, we decided to review the available data on the effects of medical cannabis on asthmatic patients.

Objectives: To review the effects of medical cannabis on asthmatic patients.

Methods: A thorough search was conducted of the MEDLINE and PubMed databases as well as the internet for publications about the effects of medical cannabis on asthmatic patients.

Results: Cannabis has a bronchodilator effect on the airways and might have an anti-inflammatory effect on asthmatic patients. However, harmful effects on the lungs are mainly attributed to smoking and include airway irritation and the development of chronic bronchitis symptoms.

Conclusions: Cannabis has some beneficial, yet many harmful effects on the lungs. Additional research is needed to determine the harmful effects of vaporizers as well as inhalers.

IMAJ 2020; 22: 232–235

KEY WORDS: asthma, bronchodilation, bronchoconstriction, medical cannabis, medical marijuana

Cannabis has been used as a source of fiber and for medicinal purposes since ancient times [1]. According to the World Health Organization (WHO), 147 million people use cannabis (marijuana); making it the world's most abused illicit substance [2].

Since the 1970s, there has been a rise in the use of cannabis for both recreational and medical purposes [3–5]. Medical research in the last century has led to a better understanding of the mechanism, pharmacokinetics, and effect of cannabis on different organs including the lungs. However, there is still much more to explore.

We present three asthmatic patients treated with medical cannabis and discuss the relevant and available literature.

PATIENTS AND METHODS

CASE DESCRIPTION

Case 1

A 30-year-old male non-smoker diagnosed with asthma, who was treated with high-dose inhaled corticosteroids, a long-acting beta agonist, and montelukast, presented to our outpatient clinic. He had been diagnosed with asthma in childhood and had recurrent exacerbations including one severe exacerbation that led to mechanical ventilation.

After using cannabis for recreational purposes, his respiratory symptoms improved. Equipped with a dozen medical references, he presented to our clinic with a request for medical cannabis.

Spirometry showed an obstructive pattern with only a 2% improvement in FEV1 after salbutamol inhalation. Later the test was repeated showing the same obstructive pattern. However, this time inhalation of 0.1 grams cannabis led to a 16% and 280 ml increase in FEV1.

After using medical cannabis inhalations through a vaporizer on a daily basis for 3 years, the patient reported no asthma exacerbations and no need for a rescue inhaler.

Case 2

A 36-year-old female who had been diagnosed with asthma in her early 20s presented with recurrent exacerbations treated every time with systemic corticosteroids. She was treated on regular basis with Fluticasone propionate/Salmeterol 250 mcg twice daily and had no history of smoking. Due to oropharyngeal thrush, she was not interested in increasing the inhaled corticosteroids dose. She asked to receive medical cannabis and the request was accepted by the Ministry of Health.

She has been treated with medical cannabis for 2 years, using a vaporizer for inhalations three to four times per week. Since the start of the treatment, she reported no further exacerbations and no need for a rescue inhaler. However, decreasing the dose of her Fluticasone propionate/Salmeterol inhaler resulted in night symptoms; therefore, she continued using 250 mcg twice daily.

Case 3

A 34-year-old asthmatic male who required a rescue inhaler at least three times per week despite using a medium dose corticosteroid/LABA inhaler presented to our clinic. Following a road

traffic accident 2 years earlier, which resulted in several fractures and chronic pain, he was treated with medical cannabis for pain management. Since the start of cannabis treatment, he reported notable improvement with his respiratory symptoms and had no need for a rescue inhaler.

LITERATURE REVIEW

Definition

Medical cannabis refers to cannabis or cannabinoids prescribed by physicians for medicinal purposes.

Cannabis is a genus of plants in the family Cannabaceae. There are three main species in the genus Cannabis: Cannabis indica and Cannabis sativa, which produces effective amounts of psychoactive cannabinoids, and Cannabis ruderalis, which has fewer psychogenic properties. Cannabinoids or phytocannabinoids are chemicals produced by the cannabis plant that have physical and mental effects when used [4,6].

The cannabis plant contains more than 500 compounds with at least 104 phytocannabinoids [6]. Two cannabinoids are produced in greater abundance than others: tetrahydrocannabinol (THC) and cannabidiol (CBD). THC, which was the first active cannabinoid discovered, is responsible for most of the psychoactive effect. CBD is less psychoactive and thought to play an important part in the anti-emetic and analgesic effect of cannabis. Several other active natural cannabinoids have been identified including CBD, CBN, THCV, CBG, and CBC [6]. Ongoing studies are exploring the effects of other cannabinoids as well.

RESULTS

HISTORY

The use of the cannabis plant as food and source of fiber dates back to 10,000 years in Taiwan. Different medicinal uses and benefits were described throughout history, including in ancient Egypt, ancient India, and ancient Greece, as well as the medieval Islamic world [1].

In the modern era, the Irish physician William Brooke O’Shaughnessy introduced cannabis to western medicine in the 1830s. After that, cannabis use increased through Europe and the United States until the end of the 19th century with the emergence of opium-derived drugs that led to a marked decline in use [1,6,7].

In the 1940s, THC was identified as the active component. In the 1970s and 1980s renewed interest in the medicinal uses for cannabis emerged, especially in the treatment of cancer and acquired immunodeficiency syndrome. Compelling medical research in the last three decades led to the legalization of medical cannabis in many countries [3-5].

MECHANISM OF ACTION

There are two primary cannabinoid receptors in the human body: CB1 and CB2. Both are part of the G protein-coupled

receptors group or GPCR. Endogenous cannabinoids, or endocannabinoids, regulate many physiological processes by activating or inhibiting the cannabinoid receptors [7,8].

CB1 receptors are mainly found in the brain and central nervous system. Activating or inhibiting CB1 receptors is thought to be responsible for the psychoactive and anti-emetic effects [6-8].

CB2 receptors are distributed through the body and immune system including the spleen and white blood cells and are thought to be responsible for modulating pain and inflammation.

In the lungs, CB1 receptors are found throughout the innervation of smooth muscles and are thought to regulate bronchial muscle tone. CB2 receptors are found on alveolar macrophages as well as T and B lymphocytes and are responsible for modulating inflammation [6-8].

FORM

Medical cannabis can be supplied as either a synthetic cannabinoid or a whole plant preparation [9,10].

Synthetic cannabinoids include [10]

- Dronabinol: a synthetic THC available as oil capsules
- Nabilone: a synthetic compound that mimics THC and is available as powder capsules
- Nabiximols: a whole plant extract containing both CBD and THC, available as a mouth spray

Whole plant preparations include dried buds/leaves, capsules, lozenges, tinctures, dermal patches, spray, cannabis edibles, and ointment [9].

Route of administration can be:

- Inhaled: through smoking dried buds/leaves, vaporizing, or via inhaler
- Oral: capsules, lozenges, edibles or sublingual drops
- Topical: oral/dermal sprays, dermal patches or ointment

Inhaled preparations are the most favorable among users as it has the fastest onset of action. In addition, the bioavailability of inhaled/vaporized THC is better than oral ranging from 10% to 35%, whereas oral bioavailability is around 6% mainly due to the first-pass metabolism [9-11].

DISCUSSION

EFFECTS ON THE LUNGS

The exact effects and mechanisms of cannabis are still not fully understood. Most of the cannabinoids have not been sufficiently researched to establish their potency and effect.

While most of the data are based on recreational cannabis users, medical cannabis has not been sufficiently studied for its effect on the lungs. The preparation technique, processing and

chemical additives can be different and can lead to different beneficial and more importantly harmful effects.

The effects of cannabis on the lungs can be divided into beneficial and harmful.

BENEFICIAL EFFECTS

- **Bronchodilation:** Several studies have shown that using cannabis, whether by inhalation or by ingestion, can acutely increase FEV1 by around 100 ml. Bronchodilation usually starts within 5 minutes after the inhalation and can last up a couple of hours. Ingesting cannabis can cause a similar but less marked effect, has a delayed onset (usually after 60 minutes), and can last up to several hours [8-12]. The proposed mechanism is that CB1 receptors in the alveolar smooth muscles cause smooth muscle relaxation and bronchodilation [13].
- **Anti-inflammatory:** Airway hyper-responsiveness, elevated serum immunoglobulin-E, airway eosinophilia, and mucus hypersecretion are characteristic of allergic asthma. THC and cannabidiol (CBD) have been shown to decrease allergen-induced mucus production in murine models [7]. Cannabinoids have been also shown to reduce allergic asthma triggered primarily by Th2 cytokines [7,12,13].
- **Anxiety:** The prevalence of anxiety and stress disorders in asthmatics is high [14,15]. Furthermore, anxiety and emotional stress are known triggers for asthma attacks. Cannabinoids are known to have both anxiolytic and anxiogenic effects [16]. Whether the anxiolytic effect of cannabis has a role in decreasing anxiety related asthma exacerbations is still undetermined.
- **Exercise-induced asthma:** Exercise is a known trigger of asthma. One study has shown a favorable effect of cannabis on exercise-induced asthma [17].
- **Smoking cessation:** Several studies including two double-blind placebo controlled studies have shown a possible beneficial effect of cannabidiol use on smoking cessation. One study showed a short-term effect of cannabidiol inhalation on decreasing the numbers of cigarettes smoked by up to 40% [18]. Another study demonstrated a reduction in the salience and pleasantness of cigarette cues, compared with placebo, after overnight cigarette abstinence in dependent smokers after a single dose of oral cannabidiol [19]. Whether these effects are sustainable for longer periods and whether the use of cannabidiol can help with long-term abstinence from tobacco smoking is yet to be established pending further research in the field.

HARMFUL EFFECTS

It is important to note that most of the available data showing harmful effects on the lungs is based on studies of recreational cannabis smokers.

- **Airway irritation and inflammation:** Cannabis smoking contains many combustion products that can irritate the airways and cause bronchoconstriction and asthma-like symptoms [12,13]. Several studies have also shown that cannabis smoking and cannabis pollen are associated with allergic diseases including allergic rhinitis, asthma, allergic conjunctivitis, and even anaphylaxis [12,20,21]. Smoking cannabis for a prolonged time has been shown to cause chronic cough, wheezing, sputum production, and other symptoms of chronic bronchitis [20-22]. Several studies have suggested that individuals smoking cannabis are at risk of developing chronic obstructive pulmonary disease and emphysema. The effect of prolonged use on lung function is still debatable with studies showing preservation of lung function and others showing a trend toward obstruction [20-22].
- **Carcinogenic potential:** Cannabis smoke, similar to tobacco smoke, contains thousands of organic and inorganic chemical compounds. Although at least 50 carcinogens have been identified in cannabis smoke, there is conflicting evidence about lung, head, and neck cancers among cannabis smokers [23,24]. This finding might be partly because many cannabis smokers also use or have used tobacco products.

While vaporizers do not have the combustion products of cannabis smoke, data on safety is still lacking. Several case reports have reported lung complications due to vaporized cannabis including airway irritation, bronchoconstriction, and pneumonitis. Although other routes of administration, including pills and edibles, are not harmful to the lungs, they have other harmful effects. Moreover, smoking and inhalation are the more favorable routes of use.

In 2019 the first metered dose medical cannabis inhaler was released following a study in hospitalized patients. Although the study showed promising results in pain management, effect on the lungs was not studied. Three of the 22 patients in the study presented with a mild cough, which resolved spontaneously within a few minutes. No other side effects were reported in this short-term study [25].

It is worth remembering that cannabis use has some other favorable and many harmful effects not related to the lungs, which are not covered in our article.

Several factors contribute to the lack of sufficient and strong evidence on the beneficial and harmful effects of cannabis on the lungs.

- Most of the available evidence is based on retrospective studies in recreational cannabis users or studies conducted on murine models.
- Concurrent cigarette smoking and other substance abuse in many studies make it harder to establish causality.

- Governmental restrictions on production and research limit the ability to conduct studies.
 - The use of whole plant preparations with different stains and different chemical concentrations makes it harder to compare data.
 - Different forms and routes of administration have different bioavailability and effects.
- Credibility in self-reporting improvement is not consistent

CONCLUSIONS

Although there is compelling evidence to suggest beneficial effects of cannabis on lung function in the short term, smoking cannabis has many health hazards related to prolonged use. Clearly, smoking of any sort should not be encouraged. However, if cannabis is used, vaporized is probably safer but does include potential side effects. Other modalities of administration lack the fast, desired onset of action and have much less bioavailability.

Much is not understood about the exact mechanisms and the active ingredients responsible for the bronchodilator effect. The anti-inflammatory and anxiolytic effects of cannabis are still not fully understood and may play a role in the asthmatic patient.

Will there ever be a cannabinoid-based inhaler for the relief/treatment of asthmatic patients? Hopefully, with time we will better understand the mechanisms and effects of cannabinoids that can perhaps lead to newer medications.

More research is needed to establish the efficacy and hazards of vaporized cannabis.

Correspondence

Dr. A. Jarjouⁱ

Pulmonary Institute, Shaare Zedek Medical Center, Jerusalem 91031, Israel

Fax: (972-2) 655-5686

email: amir_jarjou@hotmail.com

References

1. Bridgeman MB, Abazia DT. Medicinal cannabis: history, pharmacology, and implications for the acute care setting. *PT* 2017; 42 (3): 180-8.
2. Cannabis. Management of substance abuse: facts & figures. World Health Organization. [Available from http://www.who.int/substance_abuse/facts/cannabis/en/]. [Accessed 07 July 2019].
3. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Population Health and Public Health Practice; Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda. *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research*. Washington (DC): National Academies Press (US); 2017 Jan 12. 3. Cannabis: Prevalence of Use, Regulation, and Current Policy Landscape. [Available from <https://www.ncbi.nlm.nih.gov/books/NBK425763/>]. [Accessed 10 July 2019].

4. Center for Behavioral Health Statistics and Quality, 2016 National Survey on Drug Use and Health: Detailed Tables, Substance Abuse and Mental Health Services Administration, Rockville 2017. [Available from <https://www.samhsa.gov/data/sites/default/files/NSDUH-DET/NTabs-2016/NSDUH-DET/NTabs-2016.pdf>]. [08 October 2019].
5. Guy GW, Whittle BA, Robson PJ, eds. *The Medicinal Uses of Cannabis and Cannabinoids*. London: Pharmaceutical Press, 2004.
6. Thomas BF, ElSohl MA. *The Analytical Chemistry of Cannabis Quality Assessment, Assurance, and Regulation of Medicinal Marijuana and Cannabinoid Preparations*. Amsterdam: Elsevier.
7. Nagarkatti P, Pandey R, Rieder SA, Hegde VL, Nagarkatti M. Cannabinoids as novel anti-inflammatory drugs. *Future Med Chem* 2009; 1 (7): 1333-49.
8. Guindon J, Hohmann AG. The endocannabinoid system and pain. *CNS Neurol Disord Drug Targets* 2009; 8 (6): 403-21.
9. Keyhani S, Steigerwald S, Ishida J, et al. Risks and benefits of marijuana use: a national survey of U.S. adults. *Ann Intern Med* 2018; 169 (5): 282-90.
10. National Institute on Drug Abuse (NIDA). Marijuana. Last updated 2018. [Available from <https://www.drugabuse.gov/node/pdf/1380/marijuana>]. [Accessed 06 August 2019].
11. Gaston TE, Friedman D. Pharmacology of cannabinoids in the treatment of epilepsy. *Epilepsy Behav* 2017; 70 (Pt B): 313-18.
12. Chatkin, J.M., Zani-Silva, L., Ferreira, I. et al. Cannabis-associated asthma and allergies. *Clinic Rev Allerg Immunol* 2019; 56: 196.
13. Kempker JA, Honig EG, Martin G. The effects of marijuana exposure on respiratory health in US adults. *Ann Am Thorac Soc* 2015; 12: 135-41.
14. Katon WJ, Richardson L, Lozano P, McCauley E. The relationship of asthma and anxiety disorders. *Psychosom Med* 2004; 66 (3): 349-55.
15. Cooper CL, Parry GD, Saul C, et al. Anxiety and panic fear in adults with asthma: prevalence in primary care. *BMC Fam Pract* 2007; 8: 62.
16. Kamal BS, Kamal F, Lantela DE. Cannabis and the anxiety of fragmentation—a systems approach for finding an anxiolytic cannabis chemotype. *Front Neurosci* 2018; 12: 730.
17. Kennedy MC. Cannabis: exercise performance and sport. A systematic review. *J Sci Med Sport* 2017; 20 (9): 825-9.
18. Morgan CJ, Das RK, Joye A, Curran HV, Kamboj SK. Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings. *Addict Behav* 2013; 38 (9): 2433-6.
19. Hindocha C, Freeman TP, Grabski M, et al. Cannabidiol reverses attentional bias to cigarette cues in a human experimental model of tobacco withdrawal [published online ahead of print, 2018 May 1]. *Addiction* 2018; 113 (9): 1696-705.
20. Stokes JR, Hartel R, Ford LB, Casale TB. Cannabis (hemp) positive skin tests and respiratory symptoms. *Ann Allergy Asthma Immunol* 2000; 85 (3): 238-40.
21. Self TH, Shah SP, March KL, Sands CW. Asthma associated with the use of cocaine, heroin, and marijuana: a review of the evidence. *J Asthma* 2017; 54 (7): 714-22.
22. Ribeiro LI, Ind PW. Effect of cannabis smoking on lung function and respiratory symptoms: a structured literature review. *NPJ Prim Care Respir Med* 2016; 26: 16071.
23. Moir D, Rickert WS, Levasseur G, et al. A comparison of mainstream and sidestream marijuana and tobacco cigarette smoke produced under two machine smoking conditions. *Chem Res Toxicol* 2008; 21 (2): 494-502.
24. Hashibe M, Morgenstern H, Cui Y, et al. Marijuana use and the risk of lung and upper aerodigestive tract cancers: results of a population-based case-control study. *Cancer Epidemiol Biomarkers Prev* 2006; 15 (10): 1829-34.
25. Vulfsons S, Ognitz M, Bar-Sela G, Raz-Pasteur A, Eisenberg E. Cannabis treatment in hospitalized patients using the SYQE inhaler: results of a pilot open-label study. *Palliat Support Care* 2020; 18 (1): 12-17.

“A pedestal is as much a prison as any small space”

Gloria Steinem (born 1934), activist, editor

“It is better to know some of the questions than all of the answers”

James Thurber (1894–1961), American humorist and cartoonist