Indications for the use of cannabinoids

Indicação do uso de canabinoides

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ABSTRACT

BACKGROUND AND OBJECTIVES: The increasingly widespread use of cannabinoids in the management of acute and chronic pain generates an urgent need to study how cannabinoids act on CB1 and CB2 receptors and what their effects are on the organism. It is important to understand the difference in action between natural cannabinoids (cannabidiol, delta 9-tetrahydrocannabinol, cannabigerol, cannabinoil, terpenes) and synthetic ones, so that the appropriate choice is made in each case, and depending on the pathophysiology of pain, one or the other active is more indicated.

CONTENTS: Studies collected in the Pubmed, Cochrane Library and Web of Science databases were analyzed. These studies focus were on natural cannabinoids (cannabidiol, delta 9-tetrahydrocannabinol, cannabigerol, cannabinoil, terpenes) and synthetic cannabinoids in the use for the treatment of chronic pain, their action on the endocannabinoid system through the activation of the CB1 and CB2 receptor and their effect after activating this receptor, aiming to compile which cannabinoid is more indicated in the treatment of pain pathology.

CONCLUSION: The subject still requires much study and new articles are being published daily. The analysis of the studies must be carried out with criteria to evaluate their seriousness. The endocannabinoid system is closely linked to the treatment of chronic pain and some cannabinoids such as: cannabidiol, delta 9-tetrahydrocannabinol, cannabigerol, cannabinoil, as well as some terpenes are already considered important in the treatment of chronic pain inferring sparing effect of opioids, anticonvulsants, antidepressants among others.

Keywords: Cannabidiol, Cannabigerol, Chronic pain, Chronic pain treatment with medical cannabis, Delta 9-tetrahydrocannabinol, Synthetic cannabinoids, Terpenes.

RESUMO

JUSTIFICATIVA E OBJETIVOS: O uso cada vez mais disseminado dos canabinoides no controle da dor aguda e crônica gera uma necessidade urgente do estudo de como os canabinoides agem nos receptores CB1 e CB2 e quais seus efeitos no organismo. É importante entender a diferença de ação entre os canabinoides naturais (canabidiol, delta 9-tetrahidrocanabinol, canabigerol, canabinoil, terpenos) e os sintéticos, para que a escolha adequada seja realizada em cada caso, sendo que dependendo da fisiopatologia da dor é mais indicado um ou outro ativo.

CONTEÚDO: Foram analisados estudos coletados na Pubmed, *Cochrane Library* e *Web of Science*. Os estudos se concentram em canabinoides naturais (canabidiol, delta 9-tetrahidrocanabinol, canabigerol, canabinoil, terpenos) e canabinoides sintéticos no uso para o tratamento da dor crônica, sua ação no sistema endocanabinoide através da ativação do receptor CB1 e CB2 e seu efeito após ativar esse receptor, visando compilar qual canabinoide é mais indicado no tratamento da patologia álgica.

CONCLUSÃO: O assunto ainda requer muito estudo e diariamente novos artigos vem sendo publicados. A análise dos estudos deve ser realizada com critério para avaliar sua seriedade. O sistema endocanabinoide está intimamente ligado ao tratamento da dor crônica e alguns canabinoides como: canabidiol, delta 9-tetrahidrocanabinol, canabigerol, canabinoil, assim como alguns terpenos já são considerados importantes no tratamento da dor crônica inferindo efeito poupador de opioides, anticonvulsivantes, antidepressivos entre outros.

Descritores: Canabidiol, Canabigerol, Canabinoides sintéticos, Delta 9-tetrahidrocanabinol, Dor crônica, Terpenos, Tratamento dor crônica com cannabis medicinal.

INTRODUCTION

The comprehension of the endocannabinoid system (ECS), its receptors and its functions in the management of human homeostasis has allowed its use in various diseases. The use of medicinal cannabis grows with each new discovery regarding new

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components and benefits of this fascinating plant and the study of its action on the human body. Different cannabinoids bind to endocannabinoid receptors in different ways and produce various physiological effects.

Cannabinoids can be classified into endocannabinoids, phytocannabinoids and synthetic cannabinoids. Cannabis has been used as medicine throughout history, but its complexity and variability, quality control and lack of medical and patient education hinder its medical prescription on its use as a treatment.

CB1 receptors are present in the central nervous system (CNS), mainly: cortex, cerebellum, hippocampus, amygdala and basal and cerebellum nuclei. They are also in smaller amounts in the dorsal root of the spinal cord, in the periaqueductal gray matter and in the areas related to neuroendocrine effects of the hypothalamus.

These receptors are not very much present in the cardiorespiratory centers of the brainstem (explaining the safety of its use in relation to respiratory depression). This wide distribution of CB1 receptors in the CNS explains the diversity of effects of endocannabinoids and phytocannabinoids on cognitive processes, motor performance, regulation of emotions and pain control[1-3].

Synthetic cannabinoids should be referred to as "synthetic cannabinoid receptor agonists" (SCRA), a class of drugs distinct from plant-derived cannabinoids, as their receptor binding power is extremely strong. This binding generates greater potency and efficacy and properties similar to psychostimulants.

In Europe, in 2004, the first synthetic cannabinoids recognized as JWH-018 appeared. This compound binds to CB1 and CB2 receptors and was therefore referred to as a synthetic cannabinoid. The effect of cannabis is mainly attributed to the action of tetrahydrocannabinol (THC) on CB1 receptors in the brain. The effects of THC (and SCRA) occur due to its ability to bind to and activate central CB1 receptors[4].

Synthetic cannabinoids are full agonists of CB1 receptors. Their adverse effects are a result of maximal activation of these receptors. They can be used as medicinal therapy as well as recreationally to mimic the euphoric effects of cannabis and sold as "herbal smoking mixtures" or "herbal incense" under brand names such as "Spice" or "K2". The European Union's Early Warning System notified a total of 190 substances between 2008 to 2018 and around 280 were reported worldwide to the United Nations Office on Drugs and Crime. In recent years, synthetic cannabinoids have been associated with deaths and acute poisonings in Europe[5].

These synthetic substances are much more potent than natural cannabis, with greater efficacy, acting as full agonists at cannabinoid receptors. It is possible that, in addition to being highly potent, some also have long half-lives, with a prolonged psychoactive effect[6].

A study carried out to analyze patients with post-traumatic stress disorder (hyperexcitation, anxiety, depressive symptoms and sleep disturbances) showed that the use of cannabis and synthetic cannabinoids are efficient and better tolerated alternatives to conventional treatment with antidepressants, anxiolytics, anticonvulsants and psychotherapy techniques.

CONTENTS

This is a review of studies collected from the Pubmed, Cochrane Library and Web of Science databases, and compiled on groups of patients treated with medical cannabis versus synthetic cannabinoids. Both have been shown to be effective in reducing anxiety, modulating memory-related processes and improving sleep, but evidence is limited on their safety and efficacy[7].

Due to its high power to generate prolonged psychoactive adverse effects and with the advent of greater efficacy in the extraction of medical cannabis oil from *Cannabis sativa*, synthetic cannabis began to lose space in the commercial world and nowadays no longer represents a sales leader when compared to the natural extract.

Delta-9-Tetrahydrocannabinol (THC)

THC acts as a partial agonist of CB1 receptors, even at high doses. This is the reason why THC has low toxicity and excellent safety profile when compared to synthetic cannabinoids.

The total daily dose of THC should be limited to 30 mg/day or less, preferably in conjunction with cannabidiol (CBD), to avoid psychoactive sequelae and development of tolerance. When the patient presents psychoactivity as an adverse effect with the use of THC, introducing low doses of CBD is an effective strategy because it competes with the CB1 receptor displacing the THC molecule, thus decreasing the psychoactive effect.

THC is responsible for the psychoactive effect of the plant, resulting in euphoria, alteration of memory, mood, motor coordination, but it has a very important medicinal effect in some diseases. For the treatment of pain, for example, THC is essential. Its best-known effects are: analgesic, anticonvulsant, antineoplastic potential, antiemetic, appetite stimulant, muscle relaxant, anxiolytic, sleep inducer. In addition, it has a protective effect on neuroplasticity, being of great value for the treatment of neuropathic pain[8,9].

Cannabidiol (CBD)

Among the many cannabinoids found in Cannabis sativa, CBD stands out because it has been known for longer, is the most prescribed and with which the medical population is most familiar. CBD acts on CB1 receptors in different ways, as neutral antagonists, that is, they do not activate the receptor itself, but block the action of the agonist, preventing binding to the receptor. That is why CBD modulates the potentially toxic effects of THC. CBD also acts as an allosteric modulator, modulating the effects of the agonist on the CB1 receptor up or down. It induces a conformational change in the structure of the CB1 receptor that increases or decreases receptor activation by the agonist. Thus, the potentially toxic effects of THC are modulated and therapeutic effects potentiated[10].

CBD does not have the adverse effect profile of synthetic CB1 blockers, such as Rimonabant, despite being a functional CB1 receptor antagonist. This is due to the potency with which it binds to the receptors. The mechanism of action of phytocannabinoids on endocannabinoid receptors has been safer and

more effective than the mechanism of action of synthetic cannabinoids on CB1 receptors. Its effects on humans are muscle relaxation, stress relief, pain relief, inflammation relief among others, such as the attenuation of anxiety and tachycardia associated with THC.

CBD, unlike THC, is less potent and may require much higher doses for its benefits. Dose titration should be done gradually with increment every 2 days, starting with low levels to avoid unpleasant side effects. Titration of any cannabis preparation should be carried out slowly over a period of up to two weeks.

Diseases such as epilepsy, palliative care, chronic pain, use in the elderly, Parkinson's disease benefit from cannabinoids associated with conventional treatment, and may even diminish the use of some drugs, reducing their use (example: decreasing doses of anticonvulsants - saving the patient from effects such as drowsiness). In cancer patients with chronic pain who need opioids, their prescription helps to diminish the dose of opioids. In these patients, they are also used for the treatment of chemotherapy-induced nausea and vomiting.

CBD, like THC, also acts on endocannabinoid receptors, influencing physiological functions. They also bind to groups of receptors, such as the opioid, serotoninergic, dopaminergic, acetylcholinergic and gabaergic systems, acting on their physiological functions. Therefore, its action on mood, appetite, sleep, memory, inflammatory processes, as well as cardiovascular and gastrointestinal functions is understood[11].

In multiple sclerosis, CBD alone is used to relieve pain and spasticity. It is indicated in neurodegenerative diseases, dermatological diseases, viral infections and other diseases. It acts on the ECS found in different areas of the nervous system, such as the basal ganglia, cerebellum and spinal cord, explaining its effects on memory, emotion, movement and pain transmission. Recent studies have highlighted that the ECS is indeed active at all levels of nociceptive transmission, preferentially targeting the affective components of pain, due to the frontal and limbic distribution of CB receptors in the brain. CB1, specifically, is defined as the receptor with the main role in the analgesic effects of cannabinoids, although CB2 also seems to be involved. CBD has begun to be used for pain of various etiologies and for this reason is one of the most widely used cannabinoids in medicine[12].

CBD should be prescribed predominantly as an oral extract during the day and consideration should be given to adding tetrahydrocannabinol (THC) in some patients who will benefit from its qualities. To add THC, the suggestion is to start with low doses and observe the effects on the patient and start gradual opioid reduction when the patient reports improvement in function, pain intensity and/or the cannabis dose is optimized. The opioid tapering scheme can be 5% to 10% of the morphine equivalent dose (MED) every 1 to 4 weeks. Clinical success occurs when there is an improvement in function/quality of life, a ≥30% reduction in pain intensity and ≥25% reduction in opioid dose used associated with fewer adverse events. Both CBD and THC have antioxidant, neuroprotective, anxiolytic, anticonvulsant and anti-neoplastic effects[13].

Cannabinol (CBN)

CBN comes from the alkalinization of Δ9- (THC) when it is exposed to ambient air, light or heat. It is a less commercially used cannabinoid, but its indication is to improve sleep induction in patients who have difficulty sleeping. Its affinity for the CB1 receptor is weak, its psychoactive effect is minimal when compared to THC (25%) and it has an anxiolytic effect. It also has anti-inflammatory, antimicrobial, analgesic, appetite stimulating and bone tissue formation inducing effects. CBN has been prescribed mainly for patients who need a sleep inducer in isolation or when the patient is already medicated with another cannabinoid[14].

Cannabigerol (CBG)

Like THC and CBD, CBG is also studied for use as a potent anti-inflammatory. CBG treatment reduces nitric oxide production in macrophages via the CB2 receptor and reduces reactive oxygen species (ROSS) formation in intestinal epithelial cells and iNOS (nitric oxide synthase in inflamed colons) expression. CBG treatment also reduces edema in the colonic submucosa, reduces intestinal inflammation and decreases neutrophil infiltration induced by dinitro benzene sulfonic acid (DNBS), as assessed by MOP[15] activity.

Its potent anti-inflammatory action has sparked interest in its use in patients with osteoarthritis of large joints, postponing surgery in older and clinically compromised patients, improving their quality of life.

The authors of the study[16] described the pharmacological properties of CBD alone and in combination with the phytocannabinoid CBG and its potential clinical applications, especially in neurodegenerative diseases. CBD and CBG have anti-inflammatory, antioxidant and anti-apoptotic properties.

There are other cannabinoids being studied extensively to verify their properties and benefits in the various diseases that affect human beings, and over time many articles have been described and more robust and better designed studies are underway.

Terpenes

Terpenes also show important physiological effects through the ECS. Where possible, in the treatment of pain, it has been decided to use full spectrum oils. The advantage is to benefit from the entourage effect, synergism of actions, to use the lowest dose, with proven efficacy. Some examples are: myrcene, which has analgesic and sedative effects; limonene, which has antidepressant and immunostimulatory properties; pinene, which shows acetylcholinesterase inhibitory potential and bronchodilator and anti-inflammatory action; and beta-caryophyllene, a selective agonist of the CB2 receptor that has strong analgesic and anti-inflammatory potential.

CB1 and CB2 receptors are found in various areas in human beings, explaining their influence on virtually all physiological and pathological processes. The ECS acts in the protection and development and/or progression of cardiovascular, neuropsychiatric, immunological and gastrointestinal disorders.

Research in animal models of migraine, fibromyalgia and Crohn's disease confirms that the target organs of these disorders (brain, musculoskeletal system and intestine) express below-average le-

vels of anandamide and/or 2-AG, reinforcing the concept that these pathologies present an imbalance of the ECS and justifying the expressive improvement of patients with these disorders when submitted to supplemental phytocannabinoid therapy. Phytocannabinoids can contribute to the treatment of numerous pathological states, helping to rebalance the ECS[17,18].

CONCLUSION

It is important to be aware of the new studies that are being published with frenetic speed, to review the criteria that were used to design them, as well as to review possible influences from the industry that have an interest in the use of cannabis medicine. The criteria for analyzing these studies must be taken into account.
After deciding how to medicate the patient, which cannabinoid to choose based on the clinical scenario, it is important to have the Certificate of Laboratory Analysis for cannabis-based products. This certificate is the way to ensure that the substance of choice for the patient is being actually used, ensuring that the plant is not contaminated, for example, with heavy metals, or infected with fungi and bacteria.
The best way to find the optimal dose for each patient is to start by titrating slowly, reviewing adverse effects and, if this occurs, reducing the dose.

AUTHOR'S CONTRIBUTIONS

Mariana Paladini
Conceptualization, Data collection, Writing - Review and Editing, Supervision.

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