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Clinical Efficacy, Current Brazilian Laws and Safety of Cannabidiol for Refractory Epilepsy Indications

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ABSTRACT

Introduction: Epilepsy is one of the main neurological diseases affecting young adults worldwide. It is characterized by the spontaneous and recurrent occurrence of brief or prolonged episodes of excessive neuronal activity, due to a state of neuronal hyperexcitability and hypersynchrony. Cannabinoids constitute a heterogeneous group of endogenous and exogenous substances that exert diverse pharmacological actions through interaction with the endocannabinoid system. **Objectives:** This study sought to discuss the use of cannabinoids in the refractory treatment of epilepsy. **Material and Methods:** This literature review was based on databases such as PubMed and Google Scholar, as well as consultations of the current guidelines of the Ministry of Health, during the period of May and June 2024. The following keywords were used: "cannabinoid", "cannabidiol" and "epilepsy". **Results:** Although the use of cannabidiol to treat epilepsies refractory to conventional pharmacotherapy is no longer a novelty, more studies are still needed to freely indicate its use. For various reasons, including the limited number of patients in each of the clinical studies, it is not possible to conclude with certainty whether it is effective on its own or whether it only has the capacity to potentiate the effect of other drugs. A review of the renowned database found that there is currently no reliable evidence to advocate the use of CBD in the treatment of epilepsy, suggesting that more careful clinical studies be carried out (multicenter, randomized, double-blind and of longer duration). **Final considerations:** Considering the scarcity of large-scale clinical studies in proportion to the long period over which cannabinoids have been used for medicinal purposes, it is necessary to consider what lies behind the difficulty of carrying out more careful studies.

Keywords: Cannabinoid, Cannabidiol, Epilepsy.

INTRODUCTION

Epilepsy is a brain disorder in which neurons (nerve cells) act irregularly and intensely. This syndrome manifests itself through constant epileptic seizures, caused by the interruption of the brain's regular functioning (1).

It is a very diverse disease, as it can occur in various areas of the brain, and the location of each discharge will generate a different symptom or clinical manifestation. The symptoms of the disease present themselves in different ways (1).

Epilepsy is one of the main neurological diseases affecting young adults worldwide. It is characterized by the spontaneous and recurrent occurrence of brief or prolonged episodes of excessive neuronal activity, due to a state of neuronal hyperexcitability and hypersynchrony (1).

These changes in neuronal discharges generate seizures, which can be localized, comprising one of the cerebral hemispheres (partial or focal seizures) or diffuse, when both hemispheres are affected (generalized seizures). Seizures can manifest themselves in different ways, depending on the individual's state of consciousness and the involvement of the affected hemisphere (2).

At times, a small area of the brain may be affected, generating milder symptoms that correspond to the affected part. For example, if the epileptic seizure occurs in the part of the brain that controls the movements of the left arm, it may contract and become rigid. Therefore, in partial epilepsy, the manifestations are limited to the affected area (3).

Epilepsy is a chronic disease that affects millions of people and is a cause of significant morbidity and mortality, and is one of the oldest diseases known to mankind (3).

It is estimated that 50 million people worldwide have a diagnosis of epilepsy (4).

However, the heavy burden of this disease is not evenly distributed and, according to the available data, there are disparities in the prevalence and incidence recorded around the world. Many of the differences recorded can be attributed to variations in study methodology (e.g. case definition, ascertainment) and population structure (e.g. age). The increase in prevalence and incidence may be related to factors such as low socio-economic status, limited access to healthcare and environmental exposures (4).

Prevalence or incidence may be underestimated in areas where the disease is highly stigmatized and cultural beliefs about the causes of epilepsy, or negative attitudes towards people with epilepsy, lead to the concealment of epilepsy symptoms or diagnosis (4).

Multiple seizures occurring within a 24 hour period or an episode of status epilepticus (SE) are considered a single event. Individuals who have had only febrile seizures or only neonatal seizures (seizures in the first 30 days of life), and people with acute symptomatic seizures (seizures associated with acute systemic disease, intoxication, substance abuse or withdrawal or acute neurological insults), as well as individuals with a single unprovoked seizure, are excluded from this category (4-5).

Cannabinoids are a heterogeneous group of endogenous and exogenous substances that exert various pharmacological actions through interaction with the endocannabinoid system (6).

This study sought to discuss the use of cannabinoids in the refractory treatment of epilepsy.

MATERIAL AND METHODS

This literature review was based on databases such as PubMed and Google Scholar, as well as consultations of current Ministry of Health guidelines, during the period of May and June 2024. The keywords used were: "cannabinoid", "cannabidiol" and "epilepsy". The focus of the search was articles dealing with the medicinal use of cannabinoids, particularly in the treatment of epilepsy, their mechanisms, side effects and the varieties of cannabis-based pharmaceutical products available for clinical use. The articles selected included cross-sectional studies, literature reviews and technical notes available to therapeutic communities on the drugs discussed in the text.

RESULTS

Cannabinoids are a class of chemical compounds that activate cannabinoid receptors, proteins that allow these substances to interact with cellular metabolism. More specifically with the endocannabinoid system, which acts in the regulation and balance of a series of physiological processes in our body (7).

Cannabinoids and the Endocannabinoid System. The genus Cannabis, part of the Cannabaceae family, has been known since 4000 B.C., the date of the first evidence of the plant's fiber cultivation in China during the Han dynasty. There is evidence of medicinal, recreational and religious use of the plant from 1000 BC in India, Tibet, Persia and Assyria, soon reaching Europe via the Mediterranean and persisting until modern times. After a period of decline in cannabis use at the beginning of the 20th century, followed by a worldwide process of restricting its use and cultivation, which began in the USA, a new interest in the plant emerged with the discovery of the first phytocannabinoids (8).

There are three classes of cannabinoids: phytocannabinoids, endocannabinoids and synthetic cannabinoids. Plants of the Cannabis genus contain more than 100 chemically and biosynthetically related compounds, which are collectively called phytocannabinoids (8).

Phytocannabinoids are lipophilic terpenoid compounds derived from resorcinol, which are structurally distinct from, but pharmacologically similar to, endogenous synthetic cannabinoid ligands (endocannabinoids). THC and CBD are the two major compounds in Cannabis and the main ones responsible for the plant's pharmacological actions (8).

However, other phytocannabinoids such as cannabigerol, cannabichromene, cannabivarin, tetrahydrocannabivarin, cannabichromevarin and cannabigerovarin can also exert potential therapeutic effects, as has already been demonstrated in pre-clinical and clinical studies (8-9).

The description of the best-known phytocannabinoids, notably THC, dates back to the early 1970s, followed by CBD, during which time there was a fervor to study these substances. After the slow period of publications in the late 1970s, a new interest arose after the discovery of the

endocannabinoid system in the 1990s, as well as the description of its receptors and the isolation of anandamide, one of the main endogenous ligands and integrated into human physiology in various processes (8).

The endocannabinoid system exerts important regulatory functions, particularly in the central nervous system (CNS) and immune system, making it a potential therapeutic target for various disorders, including nausea and vomiting, pain, inflammation, cardiovascular disease, glaucoma, cancer, spasticity and epilepsy.

The endocannabinoid system basically consists of CB1 and CB2 receptors, endogenous ligands, as well as synthesis and degradation enzymes (8).

Cannabinoid receptors belong to the family of G protein-coupled membrane receptors, and activation of these receptors promotes suppression of neuronal excitability and inhibition of the release of various neurotransmitters, including monoamines, excitatory and inhibitory amino acids, as well as neuropeptides (9).

The main endogenous ligands of cannabinoid receptors are ethanolamine from arachidonic acid (anandamide) and 2-arachidonylglycerol (2-AG), which are derived from long-chain polyunsaturated fatty acids, particularly arachidonic acid. However, other lipid molecules such as oleamide, O-arachidonoyl ethanolamine (virodamine), 2-arachidonoyl glycerylether (noladine) and N-arachidonoyl dopamine (NADA) also have cannabimimetic action. Endocannabinoids are produced on demand in postsynaptic neurons and act as retrograde messengers in presynaptic neuronal terminals (9) (FIGURE 1).

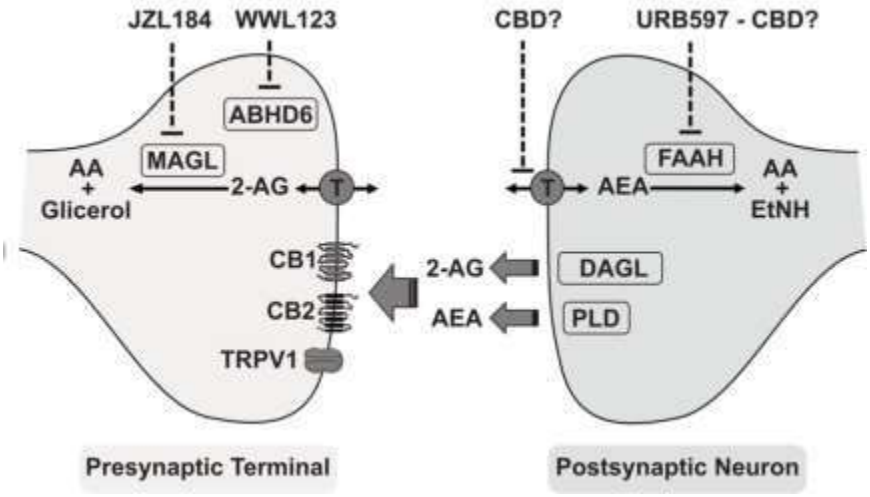
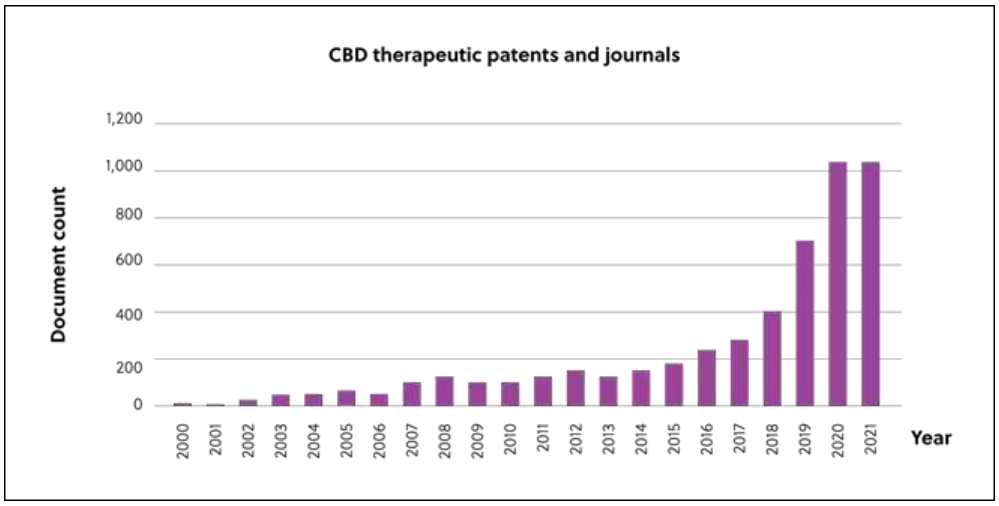


Figure 1. A simplified view of the endocannabinoid system and its main components. Endocannabinoids: Arachidonoylethanolamide (AEA, anandamide) and 2-arachidonoylglicerol (2-AG). Synthesizing enzymes: Diacylglycerol lipase (DAGL) and phospholipase-D (PLD). Membrane transporter (T). Cannabidiol (CBD) as inhibitor of anandamide reuptake and hydrolysis. Source: researchgate.net/figure/A-simplified-view-of-the-endocannabinoid-system-and-its-main-components_fig1_345808363

TRENDS IN CANNABINOID RESEARCH

Using cannabidiol (CBD) as a cannabinoid model to investigate current research into therapeutic prospects for cannabinoids has demonstrated an enormity of studies (10).

The results show that human clinical studies comprising pre-clinical documents (animal, in vivo, in vitro, ADME and in silico) have been increasing over the years, with more than 550 results (GRAPH 1). This perhaps indicates an opportunity for pharmaceutical companies, cosmetics manufacturers, nutrition organizations and other companies to further advance cannabinoid research for the benefit of humanity (10).



Graph 1. Publications (2000-2021) the number of documents organized by CAS related to the therapeutic application of cannabidiol (CBD). Statistics obtained from CAS SciFinder.

HOW CANNABINOIDS ENTER OUR BODY

There are four main routes of administration: | | Inhalation| |Sublingual | Ingestion | Topical.

One of the most popular ways of consuming cannabinoids is to smoke plant material or vaporize a cannabinoid oil, i.e. basically inhalation. When cannabinoids enter the lungs, they are quickly absorbed and also quickly eliminated from the body. Inhalation tends to be the preferred method of consuming cannabis (10).

Another route of administration is sublingual, where oils or tinctures containing cannabinoids are placed under the tongue and absorbed directly into the bloodstream. This method allows for faster and longer-lasting effects. Cannabinoids can also be ingested. The body will metabolize the edible forms, but it can take much longer to achieve the desired effects. Cannabinoids can also be used as topical agents, such as creams, lotions, sprays,patches or balms. Absorption is preferred by people who may be treating sore muscles or skin problems. Cannabinoids are absorbed through the skin directly into the bloodstream (11).

Although THC is better known, a deeper understanding of the chemical structures of non-psychoactive cannabinoids such as CBD, CBG, CBN and CBC and their effects provides insight into the emerging product landscape (8).

After THC, cannabidiol (CBD) is probably the best known cannabinoid. CBD is derived directly from the hemp plant and has no psychoactive activity. The legality of CBD is constantly changing and each (US) state has constantly evolving legislation regulating CBD. Harvard Medical School recognizes that CBD can be used to treat anxiety, insomnia, chronic pain, arthritis and addiction. More importantly, CBD is a component of FDA-approved drugs to treat severe childhood epilepsy (e.g. Epidiolex). The main side effects of CBD are nausea, fatigue and irritability (10).

Although CBG was discovered in 1964, it is used less frequently than CBD or THC because it is found in very low concentrations in the cannabis plant. CBG interacts with the cannabinoid receptors in our body, specifically CB1 and CB2. When CBG binds to these receptors, it increases neurotransmitters that affect motivation, appetite, sleep, pleasure and pain. CBG can also affect serotonin and adrenoceptors. These receptors also control neurotransmitters - CBG is sometimes called the "happiness" molecule due to the increase in neurotransmitters. Cannabigerol has been shown to have antibiotic effects and can reduce intraocular pressure in the eye (12).

Cannabinol is not synthesized directly by the Cannabis plant; CBN is a metabolite resulting from the breakdown of THC. When plant material is exposed to oxygen and time, CBN increases as THC degrades. CBN is a sedative and therefore helps with insomnia. CBN is not well researched, but some studies have shown that cannabinol has antibiotic effects, relieves glaucoma and stimulates appetite. In mice, CBN has been shown to delay the onset of Amyotrophic Lateral Sclerosis (ALS). This promising compound offers many opportunities for researchers to seek therapeutic uses for CBN (12).

CBC is derived from CBG and has demonstrated powerful antimicrobial effects, especially in infections resistant to other antibiotic treatments. In addition, some studies on mice have shown that CBC has neuroprotective effects that protect the brain from neurodegenerative conditions (Alzheimer's disease) and even stimulate the brain to develop new cells (13).

CBC does not bind well to cannabinoid receptors, but it does bind to vanilloid receptor 1 (TRPV1) and transient receptor potential ankyrin 1 (TRPA1), which are known to affect pain perception. CBC has also demonstrated anti-cancer properties. Again, there is not much data on CBC as a therapeutic agent in human studies, but in preliminary research, the properties identified favor further investigation (13).

THE ENTOURAGE EFFECT

Many cannabis products advertise "full spectrum" CBD, which means that the product not only contains CBD, but can also contain the other cannabinoids discussed here, as well as terpenes, essential oils and up to 0.3% THC (legislated). The use of these cannabinoids together to increase potency and efficacy, while differing from the effects of each chemical on its own, culminates in a theory called the "Entourage Effect" (11).

The proposed mechanism of the Entourage Effect involves inactive lipids combined with exogenous cannabinoids that increase the activity of endogenous cannabinoids (anandamide and 2-arachidonylglycerol). Research is new in this area, but some studies have shown positive results in cancer, mood and anxiety disorders, movement disorders, and epilepsy (12).

FUTURE OUTLOOK AND IMPACT

Cannabinoids have a bad reputation because of their association with marijuana and the psychoactive effects of THC and its derivatives. Legal concerns may dissuade researchers from pursuing cannabinoid research. However, early studies on cannabinoids have clear data that there may be potential therapeutic benefits to these compounds, both as single components and through the activation of our endogenous cannabinoids and the "Entourage Effect". This blog has covered just a few of the best-known cannabinoids, but remember that there are over 100 of these compounds identified and more to be discovered! Hopefully, as research continues, the stigma surrounding these cannabinoid substances will dissipate and their full potential can be used to treat debilitating diseases (13, 14, 17).

The emerging trend of increased research into recreational drugs for health benefits goes far beyond cannabinoids, see how psychedelics such as LSD, MDMA and "mushrooms" could be next in the fight against depression and PTSD (15).

TABLE 1 presents the potential therapeutic effects of cannabinoids in human and mammalian models of cannabinoid use.

Table 1. Potential therapeutic effects of cannabinoids.

THERAPEUTIC POTENTIAL	CBD	CBG	CBN	CBC
Antimicrobial		X	X	X
Antitumor				X
Anxiety	X			
Mood stabilizer		X		
Appetite stimulant		X	X	
Anticonvulsant	X			
Movement disorders	X			
Pain	X	X		X
Sedative			X	
Insomnia		X	X	
Neuroprotective				X
Arthritis	X			
Addiction	X			
Glaucoma		X	X	

Source: scientific-trends-cannabinoid-research

EFFECTS OF CANNABIDIOL IN PATIENTS WITH EPILEPSY

The first clinical study to demonstrate the anticonvulsant effect of cannabidiol was conducted in Brazil by the group of renowned researcher Dr. Elisaldo Carlini. This double-blind study was carried out with 15 patients who suffered at least one generalized seizure a week, even though they were receiving some other anticonvulsant (phenytoin, primidone, clonazepam, carbamazepine, trimethadione and/or ethosuximide) (15).

In total, 8 patients received between 200-300 mg/day of pure CBD orally for 8 weeks. Of these patients, only one did not experience any clinical improvement. Among the others, four had their seizures completely abolished during the period they took CBD and three had a significant reduction in seizure frequency. In the group of patients who received placebo together with their other anticonvulsant, only one showed improvement. However, there is no evaluation of the effect of CBD in the absence of any other anticonvulsant, but the study suggested that CBD could be an adjuvant in the treatment of epilepsy (9).

There is a great deal of evidence regarding the therapeutic potential of the two main compounds present in plants of the Cannabis genus - cannabidiol and Δ-9-tetrahydrocannabinol - especially in relation to their clinical relevance in the treatment of epilepsy. Anecdotally, standardized extracts with a high cannabidiol content have been shown to be effective in reducing the frequency and severity of seizures, particularly in children with rare types of epilepsy that are refractory to conventional drugs. This evidence has motivated the regulation of the clinical use of standardized extracts containing cannabidiol for the treatment of severe cases of epilepsy (14).

The term "medical cannabis" or "medical marijuana" refers to the use of parts of cannabis or cannabinoids derived from the plant to treat or alleviate the symptoms (pain, spasticity, nausea and vomiting) of a specific disease. Some countries, such as Canada, the USA and the Netherlands, have herbal products and pharmaceutical preparations derived from cannabis for medicinal use, as well as allopathic medicines (TABLE 2).

Table 2. Cannabinoids derived from Cannabis and synthetic products available for medicinal use.

Cannabinoids	Trade name	Route of administration	Therapeutic indication	Country of availability
22%: <1% (THC:CBD)	Bedrocan®	Vaporization, oil, tea	Nausea, vomiting, anorexia, glaucoma	Canada, Netherlands, Germany, Italy, Finland
13,5%: <1%(THC:CBD)	Bedrobinol®	Vaporization, oil, tea	Nausea, vomiting, anorexia, glaucoma	Canada, Netherlands, Germany, Italy, Finland
14%: <1%(THC:CBD)	Bedica®	Vaporization, oil, tea	Nausea, vomiting, anorexia, glaucoma	Canada, Netherlands, Germany, Italy, Finland
6,5 %: 8%(THC:CBD)	Bediol®	Vaporization, oil, tea	Neuropathic pain, inflammatory diseases, epilepsy	Canada, Netherlands, Germany, Italy, Finland
0,4%:9%(THC:CBD)	Bedrolite®	Vaporization, oil, tea	Neuropathic pain, inflammatory diseases, epilepsy	Canada, Netherlands, Germany, Italy, Finland
0 %: 98 % (THC:CBD)	Epilodex®	Solution oraL	Rare epilepsies (e.g. Lennox-Gastaut and Dravet syndromes)	Multicenter phase III clinical studies *

Source: https://clinicaltrials.gov

It is important to emphasize that the side effect profile of CBD is not the same as that expected with the use of THC and its analogues (16). In addition, the risk of developing dependence could be a limiting factor for clinical use, particularly of CB1 receptor agonists (6).

ADVERSE EFFECTS

The main adverse effects of cannabinoids in clinical use are Neurological: Altered short-term memory; reduced ability to maintain concentration, drowsiness, blurred vision, ataxia, dizziness. Psychological: Changes in behavior and mood; suicidal ideation, hallucinations, paranoia, depression, euphoria, dysphoria, psychosis, anxiety and dependence. Cardiovascular: Palpitation, tachycardia, syncope, vasodilation with decreased blood pressure (externally manifested by red eyes) and postural hypotension. Gastrointestinal: Changes in appetite, nausea, abdominal pain. Other: Weakness, fatigue, vasovagal symptoms. Risk of psychosis, particularly in individuals with a family or personal history of psychiatric illness. Risk of addiction. Cardiovascular diseases such as severe ischemia, heart failure and arrhythmias. Renal and hepatic insufficiency (20, 21,22).

BRAZILIAN LEGISLATION

Currently, no drug containing cannabidiol or any other cannabinoid has been registered for clinical use in Brazil. However, in May 2015 ANVISA published Resolution No. 17, establishing criteria and authorizing the import of cannabidiol-based products for exclusively therapeutic use in selected cases, provided they are prescribed by a legally qualified doctor (11).

The Brazilian Academy of Neurology stated that the data currently available in the literature is not sufficient to support the use of cannabidiol as a routine treatment for epilepsy, but that it could be effective in refractory or difficult-to-treat cases. He also stressed that more studies need to be carried out to establish the safety and efficacy of cannabidiol (8).

USE OF CANNABINOIDS IN MEDICAL TREATMENT - SUPPLY BY THE BRAZILIAN STATE

Excerpts quoted in full; Last modified: 06/02/2024 Topic updated on 13/12/2021."The principle of the dignity of the human person, set out in Article 1, item III, of the Federal Constitution (CF/88), elevated to the foundation of the Brazilian Republic, constitutes the framework of fundamental rights and guarantees, including social rights, provided for in Article 6 of CF/88, which guarantees everyone, among other rights, the right to health.

(...) Although the medicine that the defendant needs - CANABIDIOL EVR 22% - is not specifically established by the public network, organized in the Unified Health System (SUS), in the list (RENAME) that guides the provision of the public health service, this fact in no way exonerates public entities from their responsibility to supply the product that the defendant demonstrably needs.

Given that the treatment was indicated by the medical professional accompanying the patient, due to the unsuccessful use of other therapeutic alternatives, and given that ANVISA itself has already recognized the effectiveness of the substance in controlling the illness affecting the plaintiff, the state's duty to take the necessary measures to protect the health of the minor has been established, and it must supply the medication requested." Ruling 1166414, 07030637320178070018, Rapporteur: ROBERTO FREITAS, First Civil Chamber, judgment date: 10/4/2019, published on PJe: 29/4/2019.

EXCERPT FROM JUDGMENT

"(...) although CANABIDIOL is not registered with ANVISA, there is a Resolution of the Federal Council of Medicine (nº 2.113/2014) approving the use of this substance for the exclusive treatment of epilepsy in children and adolescents refractory to conventional treatments.

Allowing the drug to be imported and prohibiting its supply to patients who depend on the Unified Health System would be a step backwards and would only harm the poorest sections of society, and it is up to the law enforcer to remove the rigor of the rule when there is a real possibility of causing damage to a greater legal asset, namely the life, health and physical integrity of a child.

Thus, once the conventional clinical protocols for the treatment of the pathology affecting the plaintiff have been exhausted, as well as ANVISA's authorization to import the desired drug, the formal requirements are deemed to have been met, even if the drug is not registered with the supervisory body (...).

This being the case, anyone suffering from any illness has the right to demand measures from the public authorities with a view to maintaining their health, and it is unacceptable for the body responsible for registering the drug to choose the best time to adopt this procedure and grant those who can import it access to health, leaving the most needy section of society unassisted.

Ruling 1147604, 20160110915513APC, Rapporteur: CARLOS RODRIGUES, Sixth Civil Chamber, judgment date: 23/1/2019, published in DJe: 5/2/2019.

IMPORTATION OF CANNABIDIOL - TREATMENT PAID FOR BY PRIVATE INDIVIDUALS

"II - At the origin, this is a lawsuit filed by the parents of a minor suffering from severe cerebral palsy, who after several unsuccessful treatments, had news about the use of cannabidiol, associated with treatment for epilepsy, with effective improvement in the symptoms of the disease. III - Faced with the unavailability of this medication in the public network, the parents themselves arranged for it to be imported, asking the Federal Government and Anvisa to refrain from "destroying, returning or in any other way causing the cannabidiol" not to reach its destination." RESP 1657075 / PE

FINAL CONSIDERATIONS

Although the use of cannabidiol to treat epilepsies refractory to conventional pharmacotherapy is no longer a novelty, more studies are still needed to freely indicate its use. For various reasons, including the limited number of patients in each of the clinical studies, it is not possible to conclude with certainty whether it is effective on its own or whether it only has the capacity to potentiate the effect of other drugs.

A review of the renowned Cochrane database found that there is currently no reliable evidence to advocate the use of CBD in the treatment of epilepsy, suggesting that more careful clinical studies be carried out (multicentre, randomized, double-blind and of longer duration).

Considering the scarcity of large-scale clinical studies in proportion to the long period over which cannabinoids have been used for medicinal purposes, it is necessary to consider what lies behind the difficulty of carrying out more careful studies.

It is possible that aspects of legislation (peculiar to each country) as well as the undesirable effects associated with cannabinoids and finally the stigma generated in society as a result of the recreational use of cannabis may have contributed greatly to this

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