Chapter 36
Medicinal Use of Cannabis: Evidence and Therapeutic Implications

Anderson Nazareno Matos

Introduction

It is impossible to deny, there is more and more discussion on marijuana nowadays. Several countries are regulating domestic markets and offering new universes regarding the possible uses of the plant. The West experiences adult, medicinal, and industrial use in different degrees of freedom. Uruguay was a pioneer in 2013 in an experiment in which the state regulates the production process, allowing self-cultivation and cooperative clubs, as well as sale in pharmacies for adult use. All the planned stages were implemented, although curiously the regulations for medicinal use were not made, which was the way most of the countries that raised the issue began to address it. The North American scenario has also changed a lot, thirty-four states have already authorized medicinal use, and ten of them also include social use. Canada began regulating the medicinal use of cannabis in 2001, and in October 2018 it began regulating social use. In Latin America, there is the following scenario; in Brazil and Venezuela it is possible to import extracts and oils, in Chile there is cultivation in associations for medicinal use, Argentina and Colombia are preparing for the cultivation and national sale of medicinal products, Paraguay is authorizing the importation of seeds for cultivation.

What would have happened to this anti-magnet climate review? It seems possible to say that the rediscovery that the plant has several therapeutic properties and possibilities of safe use in the medical clinic has led to a resumption of research with cannabis, this would be a relevant factor in the new scenario. It also seems necessary to point out that there is a great popular pressure, mainly coming from family members and patients with serious disorders, mostly refractory to conventional treatments, which has required doctors to use marijuana products. The demand of patients on physicians has induced the medical class to review concepts and update

A. N. Matos (✉)
Conselho Regional de Psicologia de Minas Gerais, Divinópolis, MG, Brazil

D. De Micheli et al. (eds.), *Drugs and Human Behavior*,
https://doi.org/10.1007/978-3-030-62855-0_36

itself in relation to the subject. The medicinal marijuana industry has produced the unusual situation of having patients teaching their doctors about cannabis treatments. These situations have occurred in several countries in the world, the best known case is probably the girl Charlotte Figi, with the diagnosis of Dravet syndrome, about 50 daily convulsions debilitated the child more and more, taking her to the limit of what reached traditional allopathic medicine. The girl's parents became aware of reports on cannabis use in these cases and were able to medicate her with extracts rich in cannabidiol (CBD) that completely changed the child's clinical picture. The oil from the strain that was used on the girl received her name, *Charlotte's Web*, and her producers "have created a non-profit organisation in Colorado to facilitate access by people with severe epileptic syndromes to quality controlled cannabis with high amounts of Cannabidiol" (Ribeiro 2014).

Another illustrative situation would be the one set by Porter and Jacobson (2013) when the authors used parents belonging to a Facebook group dedicated to share information about the use of cannabis enriched with cannabidiol to treat seizures in children who were diagnosed with Dravet syndrome, Doose syndrome, and Lennox–Gastaut syndrome as a control group for the research. The media coverage of these cases has led to renewed scientific interest in cannabis. But certainly, the cherry on the cake is not the so controversial marijuana, but the endocannabinoid system was discovered only in the 1990s. In any case it is possible to say: marijuana, the 5000-year-old novelty returns to the scene with full force.

Historical Overview

Reports of medicinal use of cannabis are millenary, dating back to 2700 years before Christ, in Pen-ts'ao ching, a pharmacopoeia attributed to Emperor Shen-Nung there are indications for cannabis in rheumatic pain, intestinal constipation, disorders of the female reproductive system, malaria, and others. In India the records date from over 1000 AC., with reports of both religious and medical use analgesic, anticonvulsant, hypnotic, tranquilizer, anesthetic, anti-inflammatory, antibiotic, antiparasitic, antispasmodic, digestive, diuretic, aphrodisiac or anaphrodisiac, antitussive, and expectorant (Zuardi 2008). For the Assyrians, since the ninth century B.C., there was the use for edema, hematomas, depression, impotence, arthritis, renal lithiasis. Avicenas, a famous Arab doctor mentions the use of cannabis since 1000 A.D., and Muslim texts highlight the use of the plant as diuretic, digestive, antiflatulent, etc. There is a report made in 1464 by Ibn al-Badri which describes a treatment made with marijuana resin for a case of epilepsy, revealing the cure of the condition and highlighting the need to maintain the use of the plant continuously for the remission of symptoms (Zuardi 2008).

The Western world became familiar with these reports of medicinal marijuana in the nineteenth century through doctors who had experiences outside their home country and who found clinical applications and forms of treatment with the use of cannabis hitherto unknown both in Europe and the USA. William Brooke

O'Shaughnessy, an Irish doctor serving of England in Calcutta, published in 1839 "On the preparations of the Indian hemp, or Gunjah," on the occasion he reviewed the literature on the plant, tested the effect on different pathologies, described experiments where he carried out evaluating the toxicity in animals, and found therapeutic effects in humans for rheumatism, convulsions, muscle spasms of tetanus and rabies. Another report that gained prominence was the work done by the psychiatrist Jacques-Joseph Moreau, better known as Moreau du Tours. Accompanying patients on trips to exotic countries, a common practice at the time, Moreau observes the use of hashish by Arabs and decides to experiment on himself and later on his students. Moreau's expectation with the drug was to investigate the genesis of mental illness. He intended to produce an "experimental psychosis" with the use of hashish. The experiments led to the publication of the book "Du Hachisch et de l'Alienation Mental: Études Psychologiques," published in 1845. These publications impacted Western medicine, mainly due to the few therapeutic options of the time for disorders such as epilepsy, spasms, tetanus, and anger.

Soon Europe and the USA experienced the spread of cannabis products, and more than a hundred scientific papers on therapeutic cannabis were published in the second half of the nineteenth century. Several laboratories began marketing cannabis extracts or dyes, for example: Merck, Burroughs-Wellcome, Bristol-Meyers Squibb, Parke-Davis, and Eli Lilly (Zuardi 2008). In 1924 Sajou's Cyclopedia of Practical Medicine produced a summary of areas where there were clinical indications for cannabis, highlighting its use as a sedative, hypnotic, or analgesic for a substantial group of diseases (Zuardi 2008).

This would have been the "boom" in medical use of cannabis in the West, it lasted until other products or technologies emerged in both pharmacy and medicine that achieved greater efficiency or safety in handling. This would have been the case, for example, with the development of vaccines for infectious diseases such as tetanus, the emergence of aspirin, or hypodermic syringes for the injectable use of more powerful analgesics such as morphine (Zuardi 2008). But there would be other details that would influence the discontinuity of medicinal use of cannabis, such as the "active ingredient" of cannabis had not been identified, the biochemical bases of its pharmacology were unknown, the extracts from the nineteenth century were not standardized in terms of composition or dosage. There were still wide variations between products without adequate quality control and inconveniences in smoked use, and oral administration was problematic, so safety for modern standards was not clearly established (Russo 2010). Thus, although there were reports of the therapeutic effects of cannabis, and it had earned a place in the conventional pharmacopoeia for some decades, ignorance of some of its properties meant that it ended up being removed from the Western medical framework, leaving the American pharmacopoeia in 1941.

But other factors also influenced the scenario, as marijuana had already entered the scope of prohibitionism, which would become increasingly upward in the twentieth century. An international agenda had already been created since the Opium Conferences in the expectation of controlling the production, trade, and sale of some products, initially cocaine, opium, and its derivatives. At the 1924 conference

in Geneva, marijuana was included in the discussions, Egyptian delegate El Guindy reported the existence of a cannabis epidemic in his country, and that the drug posed a social risk, and that it should be included in the list of substances to be proscribed. The plea received support from several delegations and led to the creation of a subcommittee to discuss the issue, composed of Britain, India, Greece, Egypt, and Brazil (França 2015). From then on, on the world stage, a climate antipathetic to marijuana arises that will gradually transform it into a drug proscribed for medicinal use and prohibited for social use.

But, the fact is, that, even receiving contraindications, the twentieth century would not see the plant disappear. The prohibition, even if it had the pretension of global reach, did not succeed, because ancestral uses, rituals, or those derived from popular practices resisted and even expanded. The counter-culture movement would make marijuana a symbol of resistance, and in the 1960s its recreational use "spread rapidly to the younger sections of the population, throughout the western world" (Zuardi 2008, p. 13). The prohibitionist climate gave more weight to the prohibition of the plant, with the Single Convention on Narcotic Drugs, promoted by the UN in 1961, and implemented in the USA by the "Controlled Substances Act" in 1970, which "gave the Drug Enforcement Administration (DEA) and the Food and Drug Administration (FDA) the responsibility to identify which substances were authorized or proscribed, according to classification in schedules I, II and III" (Pamplona 2014). Cannabis has been included in Schedule I, which characterizes drugs with no therapeutic potential and a high risk of producing addiction.

To maintain control over the plant and its prohibition, publications began to appear, and these were mainly aimed at reflecting the stance that was being built on the world stage regarding cannabis, which was the "pure and simple condemnation of marijuana as if it were an evil drug" (Carlini 2010). In an incomplete survey by the Brazilian Center for Information on Psychotropic Drugs (CEBRID) between the twentieth and twenty-first centuries, there were 470 articles made by Brazilians, 39 of them until 1955, the first being written in 1934, when the prohibitionist climate was intensifying (Carlini 2010).

The kind of focus given to marijuana will only change in the 1960s, with the pioneering work of José Ribeiro do Valle, a professor at the Escola Paulista de Medicina da Universidade Federal de São Paulo, who, through animal studies, is once again investigating the effects of cannabis extracts with the collaboration of researchers from Switzerland (Carlini 2010). But who consistently advances this research is Professor Elisaldo Carlini, who for 30 years has published no less than 57 papers, most of them in international journals (Carlini 2010).

A great leap was made in 1964 when Gaoni and Mechoulam succeeded in identifying, isolating, and synthesizing the chemical structure of Δ9 Tetrahydrocannabinol, the main psychoactive component of marijuana (Zuardi 2008). With the advancement of the studies we arrived at the discovery of cannabinoid receptors in 1988, and the endocannabinoid, anandamide, in 1992. From the moment a scientific basis was discovered it was possible to resume the use of cannabis in modern medicine (Russo 2010). Phytocannabinoids and an endogenous cannabinoid system reveals a NEW HORIZONT

Current Surveys

The discovery of the endocannabinoid system revealed the existence of natural chemical substances, it is as if the brain produced a kind of "natural marijuana." The endocannabinoid system is a neuromodulatory system consisting of two receptors coupled to protein G: cannabinoid 1 (CB1) and cannabinoid 2 receptors (CB2). CB1 receptors are located mainly in the central nervous system, in particular they are found in the cerebral cortex, cerebellum, hippocampus, and seem to play an important role in cognition, memory, learning, emotion, mood, motor activity, and motivation. In contrast, CB2 receptors are found primarily in organs and function predominantly within the immune system where they modulate cytokine release (Katzman et al. 2016).

From the cellular point of view, endocannabinoids and phytocannabinoids act on cannabinoid type 1 (CB1) receptors abundantly expressed in the brain, causing a reduction in the release of neurotransmitters and decreasing neuronal excitation. However, depending on the brain region in which the endocannabinoids are produced, they generate very different physiological effects. Some of the known functions are, for example, regulation of body temperature, regulation of appetite, reduction of pain threshold, and modulation of cognitive processes (Pamplona 2014, p. 29).

One issue that has been addressed is that the CBD is considered a beneficial molecule and THC is considered more conservative by the medical class, through the psychoactive effects known to be attributed to it, but new discoveries indicate that this may not be exactly the case:

> The CBD was initially considered non-psychoactive, i.e. devoid of brain effects. Although today it is known that this is not true […], it is true that isolated CBD does not induce the euphoric effects of THC, and still balances some adverse effects that isolated THC presents, for example, in relation to memory impairment […]. For this reason, more modern pharmacological strategies have focused on the use of a blend of THC and CBD in different proportions, to the detriment of the use of pure THC as previously thought. Pure oral THC can produce tachycardia, dysphoria, psychotic symptoms, physical and mental sedation in healthy individuals. (Pamplona 2014, p. 20).

Under the view that THC would be the "bad molecule" responsible for unwanted effects, a line of thought has focused on the idea that only CBD would be of therapeutic use, and that the absence of THC in medicinal products would be desirable. It is an idea that seems mistaken, researchers realize that the entourage effect, that is found when using the ingredients of the plant *in natura*, and not synthetic compounds, produces more beneficial effects than only the pure molecules alone, as Pamplona (2014) pointed out, reporting several adverse effects by ingesting pure THC, orally, in healthy patients.

A point that deserves attention in relation to the use of cannabis, refers to the proclaimed relationship between the use of the plant and the appearance of symptoms, psychotic symptoms, or even schizophrenia itself. Perhaps Moreau du Tours' accounts have created the basis for this hypothesis when he reports the use of hashish as an experimental psychotomimetic (Hallak et al. 2008).

Moreau located several psychological changes that could be observed under the effect of hashish; feeling of happiness, excitement and dissociation of ideas, changes in the perception of time and space, enhancement of the sense of hearing, fluctuations of emotions, irresistible impulses, delusions, and hallucinations. For Moreau some of his volunteers experienced "occurrences of delirium or real madness," which lead him to conclude that: "there is not a single elementary manifestation of mental illness that cannot be found in the mental changes caused by hashish" (Mechoulam and Parker 2013, p. 22). For Raphael Mechoulan, the discoverer of THC, this diversity of effects, contributed to confusing research on cannabis, at that time nothing was known about the molecules of the plant.

The idea that there would be a relationship between marijuana and psychosis was strongly reinforced by the first authors who talked about the plant and led researchers to try to advance more in this aspect. Professionals accompanying patients with psychotic symptoms should be concerned with making a differential diagnosis between a psychotic condition itself and an acute/transitory drug-induced psychosis. Psychotic symptoms produced by drug abuse or abstinence tend to present remission as soon as the drug is metabolized and excreted, unlike psychosis itself, which is usually longer. When psychotic symptoms occur after the use of cannabis, they usually occur acutely and soon after the use of the drug, there may be persecutory delusions and/or jealousy, anxiety, emotional lability, depersonalization, and amnesia, hallucinations are uncommon, and the pictures are usually remixed on 1 day (Hallak et al. 2008), so although it may be possible for specific psychotic symptoms to occur, it does not seem possible to say that they settle permanently. Studies that attempt to establish a causal relationship between psychosis and marijuana remain inconclusive; other studies have presented "inconsistent results in terms of differentiating or identifying a specific type of cannabis-induced psychosis" (Hallak et al. 2008).

Among attempts to explain whether there is a relationship between cannabis use and psychosis, there is the hypothesis that schizophrenic patients abuse this substance because "the occurrence of one disorder would facilitate the development of another. That is, schizophrenia could lead to substance abuse, or substance abuse could develop chronic psychosis" (Hallak et al. 2008). Another common hypothesis is that schizophrenic patients use drugs as a kind of "self-medication," also this hypothesis is controversial because it is known that "drugs such as cannabis and cocaine can exacerbate existing psychotic symptoms, precipitate the recurrence of an acute episode and cancel the effects of antipsychotic medications" (Hallak et al. 2008). However, other findings reveal that *post-mortem* studies in schizophrenic patients present a change in the cannabinoid system that occurs in schizophrenia and that is independent of recent cannabis use, that there would be a dysfunction of the endocannabinoid system, probably in a state of hyperactivity, and concluded that "the results reinforce the idea of a cannabinoid dysfunction in schizophrenia and that this anomaly would be associated with the acute phase of the disease" (Hallak et al. 2008). That is, if there appears to be some relationship between psychosis and marijuana, it appears to be more associated with a dysfunction of the endocannabinoid system itself.

Unlike the idea that cannabis could produce psychosis, it has been tested as a drug. GW Pharmaceuticals developed a study using cannabidiol in schizophrenic patients, phase II was done with 88 schizophrenic patients, who responded only partially to standard antipsychotic treatment, patients received cannabidiol or placebo in addition to their antipsychotic medication for 6 weeks. Cannabidiol was consistently superior to placebo in attenuating symptoms of schizophrenia and also in not inducing serious adverse events. Among the drugs that act on the endocannabinoid system, pre-clinical studies and subsequent data point to cannabidiol as the promising compound for the treatment of schizophrenia symptoms without inducing significant side effects (Peres et al. 2016).

It is not yet clear enough whether the cannabis–psychosis relationship is primarily beneficial or harmful. Only the progress of studies can make this field clearer, apparently the conclusion that seems most plausible is the one that points out:

> The existence of a causal relationship between substance use and long-lasting psychotic disorder remains questionable. For example, if drug use was responsible for the precipitation of schizophrenia, it would be expected that there would be a large increase in cases of people with this diagnosis, since consumption has become more common in the last 30 years. However, recent detailed epidemiological reviews have shown that this is not the case (Hallak et al. 2008, p. 167).

Another field on which several hypotheses hovered would be that of the harmful effects of marijuana on the production of "brain damage." A Mexican study (Aguirre-Velázquez 2017) addressed the relationship between the plant, its components and cases of childhood epilepsy. Epilepsy is a chronic neurological disorder that usually requires the use of several associated drugs (polypharmacy). It has been estimated that more than 50 million people worldwide suffer from epilepsy, with 85% of these patients in developing countries like Mexico. About 30–35% of patients have refractory epilepsy, which is defined as a failure to respond to two or more antiepileptic drugs. There are an estimated 1.5 million patients with epilepsy in Mexico, 30% of whom are diagnosed with refractory epilepsy. Some studies conducted in that country have reported a prevalence between 1.2% and 3% of cases of Lennox–Gastaut syndrome, a syndrome that presents in 3% of childhood epilepsy cases. Infantile epilepsy begins in the first years of life and is often characterized by frequent, severe, and resistant seizures, generating delayed neurological development and deterioration of the child's quality of life, many of these cases do not respond to conventional treatments that include antiepileptic drugs, ketogenic diet, high doses of steroids, and even neurosurgery. Realizing that the indicated treatments have failed to control their children's seizures, some parents resort to alternative treatments, one of these alternative treatments is cannabis enriched with cannabidiol. In the last decade, interest in using Cannabis sativa in household products to treat various types of childhood epilepsy has emerged and evidence of its success has spread through digital media according to Gupta (Aguirre-Velázquez 2017).

Gloss and Vickrey (2014) conducted a systematic review of four articles reporting the use of cannabis and concluded that animal studies provided sufficient justification for testing in humans. However, there is still no consistent evidence on its

effectiveness and safety. Porter and Jacobson (2013) conducted an observational study of 19 children with refractory epilepsies between 2 and 16 years at Stanford University. The results of this study showed that 16 out of 19 patients (84%) had a reduced frequency of seizures with the use of cannabis sativa, other effects reported were: improved mood (79%), increased alertness (74%), improved sleep (68%), the only adverse effects reported were drowsiness (37%) and fatigue (16%). In another survey of 117 parents of children with refractory epilepsy, with a primary diagnosis of Lennox–Gastaut syndrome, with the presence of many spasms, Hussain et al. (2015) reported similar improvements over an average treatment time of 6.8 months using a mean dose of 4.3 mg/kg/day of cannabidiol (CBD). Devinsky et al. (2018) recently published the results of an FDA-approved open-center prospective clinical trial using a pharmaceutical product (Epidiolex) that is 99% CBD and reported a mean reduction in motor crises of 36.5% in the 162 children studied and an adequate safety profile for CBD was observed (Aguirre-Velázquez 2017).

Topics of Interest

In this work we highlight aspects related to psychiatric or neurological conditions. The choice was made because of the importance of this information, unknown to the majority of the public not affectionate to the subject, and which point to the possibility of questioning widely disseminated information on cannabis, such as that marijuana would cause schizophrenia, or that the use of cannabis would be particularly harmful to brain tissue. There are works that go in another direction, as some authors we have found point to the use of CBD as an antipsychotic:

> After some individual treatment attempts, the first randomized, double-blind, controlled clinical trial demonstrated that in acute schizophrenia cannabidiol exerts antipsychotic properties comparable to the antipsychotic drug amisulpiride and is accompanied by a placebo-like superior side effect profile. Since clinical improvement by cannabidiol has been significantly associated with high levels of anandamide, it seems likely that its antipsychotic action is based on mechanisms associated with increased anandamide concentrations (Rohleder et al. 2016, p. 1).

Regarding the possible damage to the brain, it is also possible to find divergent information, because some studies locate the possibility of neurogenesis from the use of cannabinoids.

> In recent years, considerable data have indicated that the endocannabinoid system plays a central role in neurogenesis […] activation of CB1 is necessary for axonal growth response […], the endocannabinoid system drives proliferation of neural progenitor cells […], cannabinoids actually promote neurogenesis. (Mechoulam and Parker 2013 p. 29.)

A large number of possibilities of using the plant in other pathologies must be considered, escaping the scope of this work to reach them on this occasion. As mentioned above, we have chosen to highlight only two types of disorders, belonging to the field of neurology and psychiatry, environments in which a number of

controversies have reigned, with all sorts of captious information guiding for a long time the debate on the therapeutic or medicinal use of marijuana. Thus, it seemed appropriate to point out how wide and still unknown this universe is.

Final Considerations

The current Brazilian scenario, at the time of this work, is refractory, not very sensitive to these new findings in relation to marijuana, the debates, the legal norm, or even the access of patients to these therapies continue to be conducted by a conservative view, not very sensitive to reality. However, in spite of the internal environment, which is unfriendly to the signs that global reality reverberates over the plant, in countries where the climate is more pragmatic, companies are searching for millionaire figures from the regulated cannabis market, be it for adult or medicinal use.

At some point it seemed possible to think that advances in cannabis medicine would meet with great resistance from Big Pharma, which dominates the allopathic market. The conventional market would apparently have good reason to reject the presence of cannabis for several reasons, namely being a herbal medicine product, presenting wide therapeutic coverage without the important presence of undesirable side effects, the low toxicity, the possibility of making a very specific fine adjustment in the use of dosages, etc. But, the scenario has shown that what really happened was the emergence of cannabis pharmaceutical laboratories. Companies based in countries such as the USA, Canada, Israel, Holland already offer a wide range of products, with different delivery routes for the active ingredients, serving patients in the most diverse age groups, covering increasingly larger groups of disorders. These companies already export products, serving markets that do not yet have regulations that allow local production of cannabis or derivatives, as is the case in Brazil. In fact, these companies are already starting to set up commercial representation in these countries to remedy local demands. A report produced by The Green Hub highlights that: "With a population of more than 200 million people, the market for medicinal cannabis in Brazil may become substantial even in the context of relatively restrictive regulation" (The Green Hub 2019). Complementing the scenario immediately below:

> According to the 2016 Global Health Disease Study, one in five adults in Brazil suffer from back and neck pain, meaning that the decision to include or not include chronic pain as a clinical condition in a future medicinal cannabis program could have an influence as a determinant of patient size and population increase (The Green Hub 2019, p. 2).

And a little further on, the following projections emerge:

> If Brazil passes legislation favorable to medicinal cannabis, the number of patients could reach 959,000 in the first 36 months of legal cannabis sales in the case of a more restrictive list of approved diseases (i.e. a list that does not include chronic pain), and approximately 3.4 million in the case of a broader list of diseases and clinical symptoms that includes chronic pain. The program in which chronic pain is accepted as a condition for treatment, with the number of patients able to reach 3.4 million, could mean approximately R$4.4 billion (or US$1.4 billion) in annual revenues (The Green Hub 2019, p. 3).

Thus, the current scenario is slipping. Cannabis pharmaceutical groups are already emerging, foreseeing billionaire collections for the sector. Countries that have already made their laws and regulated markets more flexible have access to yet another therapeutic option for doctors and patients, improving with palliative care the quality of life of these patients and their families, in addition to the possibility of carrying out research with increasingly better parameters, and using products with safety and effectiveness, among other advantages. This reality is already a path without a return, cannabis is able to improve the quality of life of children in complex epileptic or autism, young and adults who have suffering of the type; anxiety, depression, psychotic symptoms, or even allergic or inflammatory symptoms that affect all ages, a very large number of elderly will reap benefits in degenerative diseases.

References

Aguirre-Velázquez, C. G. (2017). Report from a survey of parents regarding the use of cannabidiol (medicinal cannabis) in Mexican children with refractory epilepsy. *Neurology Research International., 2017*, 2985729. https://doi.org/10.1155/2017/2985729.

Carlini, E. A. (2010). A História da Cannabis Sativa L. (maconha, liamba, diamba, fumo de Angola, etc.) no Brasil. In *Centro Brasileiro de Informações sobre Drogas Psicotrópicas, Simpósio Internacional: Por uma agência brasileira da cannabis medicinal?* Retrieved from https://www.cebrid.com.br/wp-content/uploads/2012/10/Simpósio-Internacional-Por-uma-Agência-Brasileira-da-Cannabis-Medicinal.pdf

Devinsky, O., Verducci, C., Thiele, E. A., Laux, L. C., Patel, A. D., Filloux, F., et al. (2018). Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. *Epilepsy & Behavior, 86*, 131–137. https://doi.org/10.1016/j.yebeh.2018.05.013.

França, J. M. C. (2015). *A história da maconha no Brasil*. São Paulo, Brazil: Três Estrelas.

Gloss, D., & Vickrey, B. (2014). Cannabinoids for epilepsy. Cochrane database of systematic reviews, Wiley, Hoboken, NJ (3). doi:https://doi.org/10.1002/14651858.cd009270.pub2.

Hallak, J. E. C., Bressan, R. A., Crippa, J. A. S., & Zuardi, A. W. (2008). Cannabis e Psicose. In A. W. Zuardi, J. A. S. Crippa, & F. S. Guimarães (Eds.), *Cannabis e saúde mental: Uma revisão sobre a droga de abuso e o medicamento*. Ribeirão Preto, Brazil: FUNPEC-Editora.

Hussain, S. A., Zhou, R., Jacobson, C., Weng, J., Cheng, E., Lay, J., et al. (2015). Perceived efficacy of cannabidiol-enriched cannabis extracts for treatment of pediatric epilepsy: A potential role for infantile spasms and Lennox–Gastaut syndrome. *Epilepsy & Behavior, 47*, 138–141. https://doi.org/10.1016/j.yebeh.2015.04.009.

Katzman, M. A., Furtado, M., & Anand, L. (2016). Targeting the endocannabinoid system in psychiatric illness. *Journal of Clinical Psychopharmacology, 36*(6), 691–703. https://doi.org/10.1097/JCP.0000000000000581.

Mechoulam, R., & Parker, L. A. (2013). The endocannabinoid system and the brain. *Annual Review of Psychology, 64*, 21–47. https://doi.org/10.1146/annurev-psych-113011-143739.

Pamplona, F. A. (2014). Quais são e para que servem os medicamentos à base de Cannabis? *Revista de Biologia, 13*(1), 28–35. https://doi.org/10.7594/revbio.13.01.05.

Peres, F. F., Levin, R., Almeida, V., Zuardi, A. W., Hallak, J. E., Crippa, J. A., & Abilio, V. C. (2016). Cannabidiol, among other cannabinoid drugs, modulates prepulse inhibition of startle in the SHR animal model: Implications for schizophrenia pharmacotherapy. *Frontiers in Pharmacology, 7*, 303. https://doi.org/10.3389/fphar.2016.00303.

Porter, B. E., & Jacobson, C. (2013). Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy & Behavior, 29*(3), 574–577. https://doi.org/10.1016/j.yebeh.2013.08.037.

Ribeiro, F. T. (2014). Cannabis sativa: o que a neurociência tem a dizer. *Scientific American Mente e Cérebro, 259*, 28–37.

Rohleder, C., Müller, J. K., Lange, B., & Leweke, F. M. (2016). Cannabidiol as a potential new type of an antipsychotic. A critical review of the evidence. *Frontiers in Pharmacology, 7*, 422. https://doi.org/10.3389/fphar.2016.00422.

Russo, E. (2010). Therapeutic uses of cannabis: Lessons of the past, design for the future. In *Centro Brasileiro de Informações sobre Drogas Psicotrópicas*, *Simpósio Internacional: Por uma agência brasileira da cannabis medicinal?* Retrieved from https://www.cebrid.com.br/wp-content/uploads/2012/10/Simpósio-Internacional-Por-uma-Agência-Brasileira-da-Cannabis-Medicinal.pdf

The Green Hub. (2019). *Cannabis medicinal no Brasil: Visão geral 2018 – Resumo executivo.* Retrieved from https://cdn2.hubspot.net/hubfs/3324860/NFD-MedicalCannabisInBrazil-Port-ES-1.pdf

Zuardi, A. W. (2008). Aspectos históricos da cannabis na medicina e em saúde mental. In A. W. Zuardi, J. A. S. Crippa, & F. S. Guimarães (Eds.), *Cannabis e saúde mental: Uma revisão sobre a droga de abuso e o medicamento*. Ribeirão Preto, Brazil: FUNPEC-Editora.