CANNABINOIDES USE IN THE CONTROL OF CONVULSIVE CRISIS IN ASTROCYTOMA AFTER NEUROSURGERY: CASE REPORT

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ABSTRACT

INTRODUCTION: Astrocytomas are low-grade tumors that are refractory to drug treatment to control seizures. CASE REPORT: G.M.S, a 29-year-old man, started to suffer from depression and frequent episodes of non-rotating dizziness associated with moderate-intensity holocranial headache, with significant worsening through emotional shock. He evolved with a left facial hemiparesis. He presented with sudden fainting, decreased level of consciousness and mydriatic pupils, needing to be intubated. Cranial CT showed formation of a cystic and loculate aspect in frontotemporal right region. The neurosurgery evaluation determined the drainage and excision of the lesion, and pathological diagnosis of Grade II Diffuse Astrocytoma was confirmed. During hospitalization, the patient evolved with ischemic stroke and visual deficit in associated cortical topography. After hospital discharge, he presented episodes of generalized tonic-clonic seizures and significant cognitive impairment. He used anticonvulsants, since in-hospital, without fully mitigating crises. Due to the absence of full control, a therapeutic test was performed with CBD/THC 1:1 oil, leading to improved control of seizures. DISCUSSION: In line with findings from randomized clinical trials in the literature, it was observed that the patient in the present study showed a reduction in the frequency of seizures with the use of oil. Recent phase II clinical trials have shown positive results regarding the survival of patients with GBM after treatment with cannabinoids. CONCLUSION: Cannabinoids has resulted in a significant improvement in seizures, in addition to possible positive effects on the cognitive and social interaction of a patient with astrocytoma in a state of recovery after neurosurgery.

Keywords: Cannabinoids; Astrocytoma; Neurosurgery.

Epilepsy is a pathology that affects the cerebral cortex, highlighting the continuous predisposition to the manifestation of epileptic seizures that translate into the clinical manifestation of seizures. Such clinical manifestation generates distinct cognitive, psychological, neurobiological and social consequences for the patient.

Epilepsy/Convulsive Crisis can be classified by etiology into: genetic, metabolic, immunological, structural, infectious and idiopathic. As for the clinical classification, it is subdivided into generalized (originating in the cerebral cortex and propagated bilaterally in the brain), focal (localized in only one cerebral hemisphere or more specific location in the brain) as well as those of unknown onset.

Epilepsy is the second most common neurological disorder in young adults, after migraine (1). It is estimated that epilepsy has an average prevalence of 0.52% in Europe, 0.68% in the United States of America (USA) and reaches a maximum of 1.5% in developing countries (STRZELCZYK et al., 2008).). There are an estimated 50

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million epileptics in the world according to the World Health Organization (WHO, 2019). Currently, more than 20 drugs with anticonvulsant properties are available worldwide (3), all associated with various side effects (4) and a high financial cost. The expenditure per patient with active epilepsy corresponds to approximately $900 to $3000 per year, with this figure being seven times higher for patients with frequent seizures (5). It is estimated that only 25% of the nearly 70 million epileptics in the world have access to conventional drugs (6), and of these, 20 to 30% continue to have treatment-refractory seizures (4,6). It is important to note that these numbers have not changed significantly despite the development of new antiepileptic drugs (FRENCH, 2007).

The clinic and natural course of the disease vary according to topography, etiology, treatment and access to a specialized center, since 40% of patients are under inadequate treatment. The evolution of 60% of patients is for seizure control with one or two medications and about 10% respond to a third medication. For those refractory to conventional drugs, a ketogenic diet, surgery and lately cannabis-based medications should be considered, more specifically cannabidiol has been proving to be a good alternative, both for the reduction and control of seizures and for the improvement of psychiatric manifestations. common in epileptic patients such as anxiety, depression and psychosis (BITENCOURT, 2021).

The use of cannabidiol-based drugs has been supported by studies. Tests in animals as well as in humans denote several benefits and safety regarding the use of this drug in the control of Seizures/Epilepsy. Few and limited are the adverse effects.

Phytocannabinoids correspond to the cannabinoids of the Cannabis sativa plant, which are able to activate cannabinoid receptors mimicking the effects of endocannabinoids. The percentages of cannabinoids in the plant vary by species and molecularly, their structures do not contain nitrogen, therefore, they are not alkaloids. They are mainly lipophilic, a property that allows them to be widely distributed in the body, and together with first-pass metabolism, they contribute to their low oral absorption. (GROTENHERMEN, 2003; HUESTIS, SMITH, 2014).

Cannabinoids generally have a carbocyclic structure with 21 carbons and are usually formed by three rings, cyclohexene, tetrahydropyran and benzene. The mechanism of action of cannabinoids is associated with inhibitory G protein (PGi). Endocannabinoids, through the PGi subunit, inhibit adenylate cyclase, decreasing intracellular cAMP, as a consequence, there is a decrease in cAMP-dependent

transcription factors. Through the dimer, said receptor can also modulate ion channels, decreasing calcium influx. In presynaptic neurons, for example, inhibitory effects were observed on N-type and P/Q calcium channels, in which the release of pain-modulating neurotransmitters (glutamate) is decreased. On L-type calcium channels, in smooth muscle, its inhibitory action is correlated with vasodilatory effects; and in postsynaptic cells, they would have an effect on decreasing K+ production, increasing membrane excitability (JOHNSON et al., 2013; MACKIE, 2008).

The famous cannabidiol is chemically referred to as 2-(6-isopropenyl-3-methyl-2-cyclohexen-1-yl)-5-pentyl-1,3-benzenediol, whose formula is C21H30O2. The molecule's mechanism of action is not fully understood. CBD has been found to act primarily on a G protein-coupled receptor (GPR55) and transient receptor potential vanilloid-1 (TRPV1), in addition to inverse agonist actions on 5-HT1A (Martínez-Aguirre et al., 2020), acting on α3 and α1 glycine receptors, adenosine A1 receptor, sodium channels, increased GABAergic neurotransmission and an indirect modulation of CB1R. (JOHNSON et al., 2013; RYBERG et al., 2009; PERTWEE, 2001, GROTENHERMEN, 2004; PACHER, BÁTKAI, KUNOS, 2006; DEVINSKY et al., 2014; Britch et al., 2020; Lazarini-Lopes et al. ., 2020b).

Although the precise mechanism of action of CBD in humans remains unknown, there are several plausible targets and the preclinical evidence presented strongly implicates three molecular targets in the anticonvulsant properties of CBD: (1) CBD reduces neuronal excitability through functional antagonism of Receptors GPR55, (2) desensitization of TRPV1 receptors, and (3) inhibition of adenosine transport. (GRAY, 2020) (Silvestro, 2020)

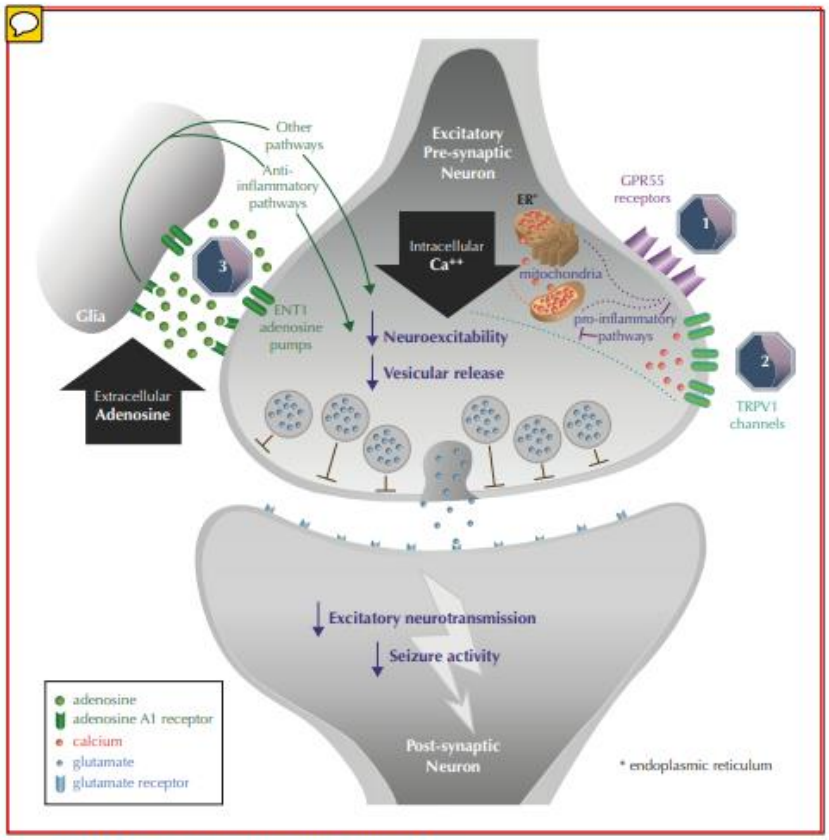

Figure 1. Proposed multimodal mechanism of action of CBD in epilepsy.

In basic research, CBD not only exerts anticonvulsant effects (Gobira et al., 2015; Kaplan et al., 2017; Klein et al., 2017; Lazarini-Lopes et al., 2020b), but also has important additional prominent effects. for the treatment of epilepsy, such as neuroprotective effects (Campos et al., 2016; Do Val-da Silva et al., 2017) and anti-inflammatory effects (Costa et al., 2004; Esposito et al., 2011). As epilepsies are often accompanied by neuropsychiatric comorbidities, it is also important to know that CBD has antipsychotic, anxiolytic, and antidepressant effects (Zuardi et al., 1991; Crippa et al., 2011; Linge et al., 2016)

In several models of temporal lobe epilepsy, an agonist of CB1 and CB2 had anti-epileptogenic effects (DI MAY 2015) and blockade of CB1 and CB2 had pro-epileptogenic effects. (VINOGRADOVA, 2011) The endocannabinoid 2-AG was up-regulated in a pilocarpine-induced model of acute epilepsy. (WALLACE 2003) These data support the hypothesis that anandamide and 2-AG are released after neuronal hyperexcitability to counteract glutamate excitotoxicity during seizures. (MARSICAN 2003) Palmitoylethanolamide (PEA) had antiepileptic effects, effects partially reversed by CB1 and CB2 antagonists (AGHAEI, 2015), these findings are in line with the idea

that PEA also acts by increasing the effects of endocannabinoids on their receptors (PETROSINO, 2017). PEA can be explored as a tool for symptoms associated with neuroinflammation in CNS disorders. In vitro, it increases CB2 expression via PPAR-α activation. (GUIDE 2017)

GABA signaling in the substantia nigra reticulum (SNr) part is thought to be an endogenous anticonvulsant system that appears to be modulated by the endocannabinoid system, especially CB1, which could be an important clue to explain the neuronal basis of cannabinoid effects. in audiogenic crises. (Lazarini 2021) Study with a single dose of CBD showed a protective effect on the epileptogenic disease process in WAR rats. (VINOGRADOVA 2015)

The location of CB1 in the brainstem and forebrain structures also supports SEC modulation in seizures, especially in the SNr, amygdala, hippocampus and cortex, the brain sites where CB1 expression is most intense.

Cannabivarin (CBDV), a CBD analogue, showed dose-dependent protective effects against audiogenic crisis in DBA/2 mice, reducing the percentage of animals that developed tonic seizures, decreasing mortality to zero and increasing the number of seizure-free animals (Hill et al., 2012)

CBD pretreatment showed a dose-response effect, attenuating seizure expression, blocking tonic-clonic behaviors and preventing seizure behaviors in more than 80% of Angelman Syndrome mice tested (Gu et al., 2019)

Current data on cannabis-derived compounds in audiogenic crises, especially CBD, CBDV and THC, are converging, suggesting attenuation of wild running and tonic-clonic behaviors in acute AS. (Lazarini 2021)

A study of male albino rats, Sprague-Dawley CDOs showed that CBDa-enriched hemp extracts exhibited dose-dependent anticonvulsant protection, but no more effective than CBD. (GOERL 2020)

The possible existence of synergistic effects between CBD and conventional anticonvulsants cannot be ignored (Gaston et al., 2017) and the promising beneficial health effects encourage many researchers to test the possible therapeutic properties in seizures using phytocannabinoids with a similar chemical structure. to THC and CBD, such as Δ8-THC, Δ9-THCB, Δ9-THCV, CBDV, CBN. The anticonvulsant properties of cannabinoids acting through different receptors and channels are described and visualized below:

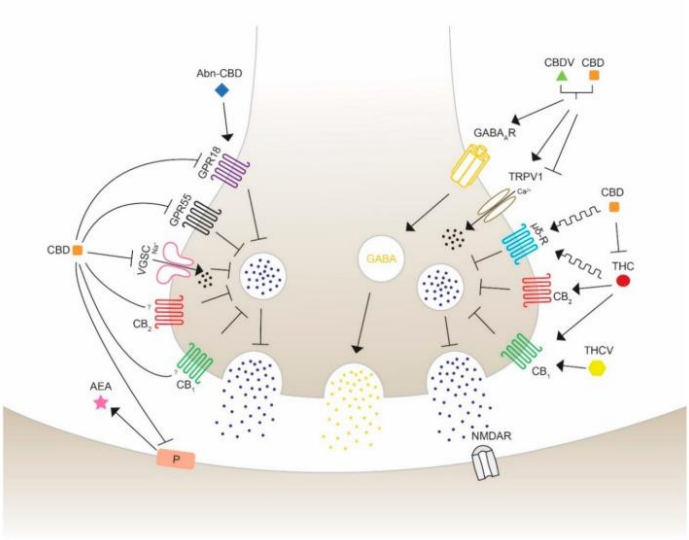

Figure 2

Schematic view of the action of different phytocannabinoids, possibly capable of modulating seizures and epilepsy. Cannabidiol (CBD) inhibits the synthesis and mobilization of N-arachidonoylethanolamide (AEA) from postsynaptic synapses, thus acting as an independent and indirect antagonist towards CB1 and CB2 cannabinoid receptors. CBD antagonizes G protein-coupled receptor activity 18 (GPR18) and 55 (GPR55) and the influx of Na+ from voltage-gated sodium channels (VGSC) to block neurotransmission activity. Abnormal CBD (Abn-CBD) acts through GPR18 to decrease intracellular Ca2+ release (left side). It is proposed that CBD and CBDV exhibit positive modulation and agonist effects at the γ-aminobutyric acid type A receptor (GABAAR), leading to an activation of GABA mobilization at inhibitory synapses. CBD and cannabidivarin (CBDV) activate and desensitize the transient vanilloid receptor potential type 1 and 2 (TRPV1/2), reducing the extracellular influx of Ca2+ and decreasing the concentration of Ca2+. (-) - trans-Δ9-tetrahydrocannabinol (THC) and CBD are allosteric modulators of the μ and δ opioid receptor, which inhibit the release of neurotransmitters to activate the N-methyl-d-aspartate (NMDA) glutamatergic receptor leading to a reduction of seizures. THC activates CB1 and CB2 leading to an inhibition of glutamate release. This action can be blocked by CBD, which is able to inhibit the THC-CB1 interaction. It is suggested that Δ9-tetrahydrocannabivarin (THCV) induces anticonvulsant activity in a concentration- and CB1-mediated manner. The exact mechanisms of activation, inhibition or modulation are still being considered. Furthermore, the different potencies of the indicated

molecules must be taken into account to correctly interpret the illustrated effects, as in the case of THC and CBD that bind to CB receptors with affinity, respectively, in the nM and mM range. (Senn. 2020)

In adult humans diagnosed with epilepsy, doses of 200-300 mg/day of CBD are well tolerated (LEO; RUSSO; ELIA, 2016). In a phase I study, with healthy volunteers, the oral administration of 3mg/kg of CBD per day, for 30 days, showed no signs of toxicity or serious adverse effects, being well tolerated (CUNHA et al., 1980). In studies of treatment-resistant schizophrenia in which the use of CBD as monotherapy was evaluated, doses of 1280 mg/day were reported to be well tolerated. No adverse effects were reported (ZUARDI et al., 2006). The results of studies for CBD, given as monotherapy, show a wide margin of safety and good tolerance, even with high doses. The presentation of adverse effects directly associated with this cannabinoid appears to be limited (FREEMAN, 2018; CHEN et al., 2018).

THC can lead to a rapid and substantial dose-dependent increase in heart rate of up to 100%, and a modest increase in blood pressure likely mediated by sympathomimetic stimulation and minor parasympathetic activity, which peaks at 15 minutes and lasts up to 3 hours. Cardiac expenditure increases by 30% or more. In addition, THC can facilitate the conduction of the atrioventricular node, reducing the time of expulsion of the left ventricle, thus decreasing the peripheral vascular resistance, mainly in the skeletal muscle, which can cause orthostatic hypotension, which can cause dizziness, syncope or lipothymia (POTTER, 2017)

Cannabis has a superior safety profile compared to many other drugs, with no reports of overdose deaths, due to a relative scarcity of CB1 receptors in cardiorespiratory brain centers (KALANT, 2004). Both receptors are G proteins with seven transmembrane domains. At the CNS level, they are found mainly in the presynaptic membrane and act in the retrograde regulation of synaptic function (HOWLETT et al., 2002; GROTENHERMEN, 2004; PACHER; BÁTKAI; KUNOS, 2006).

Emergency departments have reported overdoses with synthetic cannabinoids such as K2 and Spice, presenting with agitation, paranoia, anxiety, confusion, palpitations, hypertension, nausea, vomiting and seizures. One of the reasons for such toxicity is its potent agonist activity at the CB1 receptor due to the high level of THC in these substances. (FORD, 2017)

Human and animal studies suggest high potential for CBD to attenuate the effects of THC, in particular in decreasing the effects of THC on cognition/memory. (JACOBS 2016) In this context, CBD may provide a specific antidote to neurotoxicity with synthetics, given its anticonvulsant, sedative and antipsychotic properties. (ENGLUND 2013)

Administration of a therapeutic dose of CBD (750 mg) showed significantly low abuse potential in a highly sensitive population of multidrug users. Although high and supratherapeutic doses of CBD (1,500 mg and 4,500 mg, respectively) have detectable subjective effects compared to placebo; the effects were significantly less than those seen with alprazolam and dronabinol. (SCHOEDEL, 2018)

On the one hand, CBD enhances the therapeutic effects of THC, improving its distribution and bioavailability. On the other hand, CBD reduces the adverse effects of THC (SÁNCHEZ, 2017). This is partly due to its potent anxiolytic and antipsychotic activity, and partly to its ability to inhibit the metabolic processing of 45 THC to 11-hydroxy-THC, to which psychoactive properties greater than those of THC are attributed (MCPARTLAND; GUY; MARCH, 2014).

THC is not associated with sudden death due to respiratory depression as is the case with opioid analgesics. Long-term cognitive, psychological and endocrine effects of THC are still being investigated. As for CBD, it can be liver toxic and increases the risk of drowsiness and sedation, but the adverse effect most commonly seen in controlled clinical trials was mild to moderate. However, they require ongoing pharmacovigilance and regardless of differing views on the subject, cannabis-derived medicines need to be evaluated like any other substance in terms of quality, efficacy and safety.

A phase 1 study in 28 children diagnosed with treatment-refractory epileptic encephalopathy, recruited from 4 Canadian cities, providing full spectrum extract of the Cannabis sativa plant enriched with CBD in doses up to a maximum of 10 to 12mg/kg/day, aimed to investigate primarily safety and frequency of epileptic seizures. The preliminary results available showed tolerability of doses of 10 to 12mg/kg/day in all participants, in addition to a reduction of epileptic seizures by an average of 74% and an improvement in the quality of life score, with the greatest improvements in the cognitive functioning subscales. , social and emotional. Mild side effects of drowsiness, nausea, vomiting, diarrhea, difficulty sleeping, and spasticity have been observed. No significant changes were observed in blood count, electrolytes, renal panels,

triglycerides, cholesterol, albumin or bilirubin levels. All participants had elevated ALT at visit 1, however, these levels did not increase with introduction and titration. Levels of anticonvulsants did not change significantly and remained within therapeutic limits, with few exceptions in the use of clobazam and sodium valproate. (HUNTSMAN, 2019)

A phase I study performed with Sativex®, a cannabis-based drug containing 2.7 mg of THC and 2.5 mg of CBD per spray, in healthy volunteers, using up to 18 sprays twice a day, did not observe any changes. relevant clinical findings on QT, PR, or QRS intervals, heart rate, or blood pressure. In the case of Sativex®, used in more than 1500 participants with multiple sclerosis, in both placebo-controlled and long-term open-label studies, the most frequent adverse reactions (≥1/10) during the first four weeks of exposure were dizziness. and fatigue, usually mild to moderate and which subsided within a few days, although treatment continues. (GW PHARMACEUTICALS, 2016)

The possibility of dependence is a controversial issue, the consensus being psychological rather than physiological. It is estimated that the risk of dependence of recreational cannabis users (with a high THC content) is as high as 9%, a much lower number compared to tobacco, alcohol and other illicit drugs (ANTHONY; WARNER; KESSLER, 1994). It should be noted that, so far, no signs of dependence have been described in participants who used it for therapeutic purposes (JOHNS, 2001). On the other hand, in 2018 the WHO Expert Committee on Drug Addiction declared that CBD has no risk of generating dependence. (EXPERT COMMITTEE ON DRUG DEPENDENCE, 2018)

The most important effects of THC overdose are anxiety, hallucinations, panic attacks. Studies in which THC was administered along with opioids reported that euphoria and hallucinations decreased when THC and morphine (conjugated) were administered. Physiological parameters also showed changes depending on the medication: heart rate increased with the administration of THC alone, while blood pressure and oxygen saturation decreased after the joint administration of THC and opioid. (NAEF et al. 2003)

A number of studies demonstrate anticonvulsant properties of THC and CBD. Agonist activity at CB1 and CB2 endocannabinoid receptors demonstrated anticonvulsant effects seen with THC, however CBD shows low affinity and negative allosteric effects on them. Its antiepileptic mechanism is still unclear, but CBD has been shown to block the absorption and hydrolysis of anandamide, effectively increasing its

availability to activate CB1 and CB2 receptors so that it can modulate the activation of these receptors indirectly. Another likely mechanism is activation of the transient receptor potential (TRP) of vanilloid type 1 (TRPV1), which is also an anandamide receptor and can modulate calcium channels. (GASTON; SZAFLARSKI, 2018)

The experiment by CUNHA et. al (1980) evaluated in a first phase the use in healthy patients, without alterations in clinical and laboratory tests (EEG, blood count, bilirubin, transaminases, creatinine and urinalysis). Patients were randomized and there were no reports of any psychotropic effects and no changes in clinical and laboratory tests. In a second phase, it evaluated the electroencephalographic pattern of 15 epileptic patients refractory to conventional medication, divided into placebo and intervention groups, observing a decrease in the frequency of seizures throughout the study, with an improvement in the tracing pattern in patients using cannabidiol 200 to 300 mg per day. There was a methodological flaw regarding the statistical analysis.

The FDA has approved the drug Epidiolex® for the treatment of refractory epilepsy derived from Dravet and Lennox-Gastaut syndrome. Epidiolex® is a Cannabis extract rich in Cannabidiol with a high ratio of CBD to THC. Results from a first open-label study showed that treatment was associated with a significant reduction in seizure frequency in a high proportion of participants. The absence of seizure was observed in 9% of all treatment responders and was higher in participants with Dravet Syndrome. Furthermore, participants who responded early appear to have a prolonged seizure remission response (DEVINSKY et al., 2016). Subsequently, the results of a randomized, double-blind, placebo-controlled clinical trial continued only in participants with Dravet Syndrome. They indicated that there was a 39% reduction in monthly seizure frequency with Epidiolex® use, while the proportion of participants with a ≥50% reduction in seizure frequency was 42.6%. On the other hand, 5% of participants were seizure free (DEVINSKY et al., 2017).

Finally, the results of the last clinical study published by the same research group show a decrease in the frequency of atonic seizures of 41.9% in participants with Lennox-Gastaut syndrome who used Epidiolex® at a dose of 20mg/kg and a reduction of 37 .2% in the group that used the dose of 10mg/kg. The most common adverse effects were drowsiness, decreased appetite and diarrhea.

The researchers concluded that among children and adults with Lennox-Gastaut syndrome, the addition of cannabidiol at a dose of 10mg or 20mg/kg/day to a conventional antiepileptic regimen resulted in a greater reduction in seizure frequency

than placebo. Adverse events with Cannabidiol included elevated hepatic aminotransferase concentrations (DEVINSKY et al., 2018).

In another investigation, Israeli scientists retrospectively evaluated the effects of CBD oil on a group of adolescents and children (74 participants) with intractable epilepsy (TZADOK et al., 2016). Study participants were resistant to conventional treatment and treated for epilepsy with CBD-rich cannabis extract (20:1 CBD:THC ratio) for a period of at least three months. Research results showed that CBD treatment produced a significant positive effect on seizure frequency, with 89% of study participants reporting a reduction in seizure frequency. Of these, 18% reported a 75-100% reduction, 34% reported a 50-75% reduction, while 12% reported a 25-50% reduction, and only 26% reported a less than 25% reduction in seizure frequency. Meanwhile, only 7% of participants reported worsening seizures. Other observed results include improvement in behavior, attention, language, communication, motor skills and sleep. (TZADOK et al., 2016).

DEVINSKY et al. (2016) evaluated the percentage of monthly reduction by types of seizure, with the best response being focal seizures (55%), followed by atonic (54.3%), tonic (36.5%) and tonic-clonic (16). %). DEVINSKY et al. (2017) (21) selected patients from Dravet and found a 38.9% reduction in seizures in the cannabidiol group versus a 13.3% reduction in the control group. In the same study, 62% of caregivers reported improvement in the patient's overall impression versus 34% of the placebo group, using the Caregiver Global Impression of Change scale. Drowsiness (33%) was the main side effect, followed by diarrhea (31%) which was observed at doses greater than 15mg/kg.

The study by HESS et al. (2016) (22) analyzed patients with refractory epilepsy and tuberous sclerosis. After 3 months of CBD treatment, the response rate was 50%, with an average change in seizure frequency of 48.8%. Cognitive and behavioral improvements reported during treatment were documented through the reports of parents, who reported cognitive gains in 85.7% of cases of global developmental and behavioral delays, as well as improvements in 66.7% of cases with behavioral problems.

The study by KAPLAN et al. (2017) (23) involved patients with Sturge-Weber Syndrome, but only 5 patients were included. They were followed up for about 14 weeks. One individual withdrew for lack of response and the other four remained for more than 60 weeks. The results do not provide evidence to draw conclusions regarding

the efficacy in this group of patients, due to the non-significant sample, but suggest that CBD has good tolerability in these patients.

The experiment by THIELE et al. (2018) (24) used patients with Lennox Gastaut Syndrome and demonstrated with statistical significance a reduction in the number of monthly seizures in the CBD group, when compared to the placebo group, with a median of 41.2% and 13.7% compared to the placebo group. to the base value, respectively. One patient died, which was not attributed to the randomized clinical trial, however the author does not make clear the justification and which criteria were used to rule out a causal relationship with the outcome. Adverse effects found were drowsiness, diarrhea, decreased appetite, behavioral changes, vomiting, pyrexia, irritability, agitation, weight changes, decreased sleep quality, mental confusion, temporary increase in seizures, right eye protrusion, tiredness, epigastric pain , sweating, hepatotoxicity, gait alteration and change in the concentration of associated antiepileptic drugs.

THIELE et al. (2018) noticed more significant side effects in the group that used clobazam associated. DEVINSKY et al. (2016) (25) identified that CBD alters the concentrations of antiepileptic drugs – in this case, clobazam and valproate. There was an increase in side effects at doses above 15mg/kg/day, according to DEVINSKY et al. (2016) and 25mg/kg/day, in the study by KAPLAN et al. (2017)(26).

Regarding refractory epilepsies, a Cochrane review (GLOSS; VICKREY, 2014) concluded that the available evidence is not enough to be able to draw reliable conclusions about the effectiveness of cannabinoids in the treatment of epilepsy, due to the low number of clinical studies and not because the evidence indicates that its use is ineffective or unsafe, moreover, new studies were carried out after this review (FREEMAN, 2018; CHEN et al., 2018).

A meta-analysis evaluated 670 patients on the treatment of refractory epilepsy with cannabidiol-based products (CBD). In all, there were 11 valid references, with a mean impact factor of 8.1 from February 2017 to December 2017. There were more reports of improvement in patients treated with CBD-rich extracts than in patients treated with purified CBD ($p < 0.0001$). However, when the standard clinical threshold of a "50% or greater reduction in seizure frequency" was applied, only 39% of subjects were considered "responders" and there was no difference ($p = 0.52$) between treatments with extracts. rich in CBD and purified CBD. Patients treated with CBD-rich extracts reported an average dose four times lower than those using purified CBD.

Adverse effects were reported more frequently for products containing purified CBD than for CBD-rich extracts. In conclusion, the author (Brazilian) suggests that CBD-rich extracts appear to have a better therapeutic profile than purified CBD, at least in this population of patients with refractory epilepsy. (PAMPLONA 2018)

The fact that CBD decreases THC's ability to generate psychosis is very interesting. Furthermore, both molecules are chemically active in our body and have been used to treat various symptoms and ailments. There is controversy between those who believe that CBD should be used without association with THC and those who argue that both substances are necessary to establish an effect in our body (MCPARTLAND; RUSSO, 2001; WADE et al., 2003). Current evidence is stronger in support of this second option, considering that there is synergy not only between CBD and THC, but also between the various components of the cannabis plant, including terpenes and flavonoids. This effect, also called the "entourage effect" is what explains the greater effectiveness observed with extracts from the whole plant in relation to the pure components extracted from it or from synthetic cannabinoids (MCPARTLAND; RUSSO, 2001; WADE et al., 2003; RUSSO). et al., 2011; DACH, MOORE, KANDER, 2015).

While CBD (Epidiolex) has been shown to be effective against Dravet syndrome in a clinical setting, there are suggestions that products with a little THC are better at controlling flare-ups than CBD alone. (MECHOULAM, 2017).

Regarding the synergistic effect of an extract derived from the whole plant and the safety of CBD in epilepsy, the inclusion of THC in the formulation can improve the effectiveness profile of CBD and therefore reduce the dose required to show positive effects in controlling epilepsy, thus decreasing the occurrence of adverse effects associated with high doses of CBD. (ROSENBERG et al., 2015) The pharmacodynamics of THC and CBD show that THC agonist activity at CB1 and CB2 endocannabinoid receptors has anticonvulsant effects, however CBD shows low affinity and negative allosteric effects on them but blocks the absorption and hydrolysis of anandamide, the analogue endogenous THC, increasing its availability to activate CB1 and CB2 receptors; therefore, CBD can indirectly modulate the activation of these receptors at glutamatergic synaptic terminals (ABRAMOVICI et al., 2018).

Furthermore, with regard to the safety of THC, in addition to the negative allosteric effect of CBD on CB1 receptors, CBD has been shown to inhibit the

hydroxylation of THC to its primary psychoactive metabolite 11-hydroxy-THC, which may also help to reduce the psychoactive effects of THC. (HLOžEK et al., 2017).

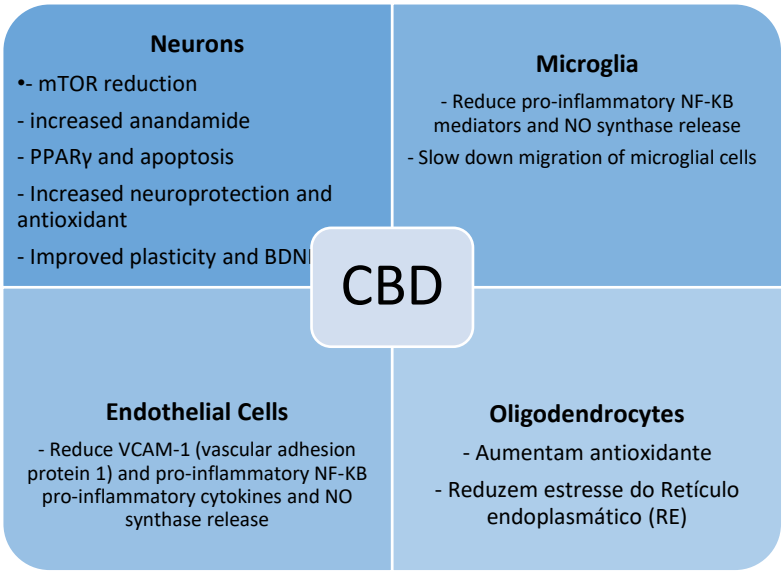

Figure 3. Cellular Benefits of CBD on the Central Nervous System (CNS). (Source: adapted from Marron & Bost, 2018.)

The percentage of absorption of cannabinoids depends on their route of administration. After oral administration of THC, studies report a bioavailability of 6%, compared to 27% when inhaled. After smoking a cigarette, the detection of THC and CBD in plasma is immediate, while when administration is performed orally, peak concentrations occur between 1-5 hours (KARSCHNER et al., 2010). The percentage of bioavailability of THC varies between 2 and 56% and that of CBD between 11 and 45% (KARSCHNER et al., 2010). This percentage of absorption (of 28 cannabinoids in general) has a high intra-subject variability, for example, variations in the concentration of THC in the blood obtained after inhaling a cigarette, which vary according to the depth of inhalations, resistance and subject's expectation, etc. (HUESTIS, 2007). Excipients were found to be important, since sesame oil improves the bioavailability of THC when administered orally (ANGEL ARÉVALO-MARTÍN, 2002).

Presentations for oral (oral/sublingual mucosa), cutaneous and rectal atomizer administration are made to improve bioavailability and avoid first-pass metabolism. Reports for rectal presentations have shown bioavailability approximately double that obtained with oral presentations (HUESTIS, 2007). Pharmacokinetic studies support this administration through the oral mucosa, it seems to be the most recommended to achieve a balance between absorption rate, plasma levels and the incidence of adverse effects.

THC and CBD, as well as most of their metabolites, are highly lipophilic, distributing and accumulating widely in tissues. Therefore, these and other cannabinoids are absorbed orally more efficiently if combined with fatty foods and to a lesser extent when dissolved in ethanol. The blood-brain barrier plays an important role in acute exposure to THC by preventing its accumulation. This mechanism would be lost as a result of deregulation in chronic consumers (HUESTIS, 2007).

THC is highly bound to plasma proteins (95-99%), mainly lipoproteins, and only 5% or less circulates in the blood in the free form. It is highly lipophilic, so it binds to various tissues, especially the most vascularized, and in particular to adipose tissue, reaching a low concentration in the brain. This is how only 1% of THC administered intravenously is in the brain at the time of maximum psychoactivity (HUESTIS, 2007).

THC crosses the placenta and passes into breast milk. Concentrations that reach the fetus are about 10% of the mother's serum concentration when administered orally and up to 30% when administered by inhalation. In breast milk, the concentration can be 8.4 times higher than in maternal plasma (GROTENHERMEN, 2003).

CBD does not affect THC metabolism at low doses of 5mg, however it can change it at high doses ≥15mg. (KARSCHNER et al., 2010).

Cannabinoids are slowly eliminated as a result of their accumulation in tissues. Furthermore, in the case of THC, the elimination half-life of the metabolites is longer than the elimination half-life of the precursor molecule. Between 80-90% of THC is excreted after 5 days, 65% in faeces and 20% in urine. THC metabolites can be detected in urine up to 18 days later in occasional users and up to 46 days later in regular users.

The half-life (t1/2) of CBD was reported as 1.1 and 2.4 h after nebulizer and aerosol administration (20 mg), 1.09 and 1.97 h after single oral administration (10 and 20 mg) 2.95 and 3.21 h after 10 mg oral lipid capsules, between 1.44 and 10.86 h after administration of mucosal oral spray (5–20 mg), 24 hours after intravenous administration, 31 hours after inhalation and 2 to 5 days after chronic oral administration (MILLAR et al., 2018). The elimination phase of THC can be described using a two-compartment model with an initial half-life (alpha) of approximately 4 hours and a terminal half-life (beta) of 25 to 36 hours. (GROTENHERMEN, 2003).

THC and CBD are metabolized by the cytochrome P450 enzyme system. Concomitant treatment with the CYP3A4 inhibitor, ketoconazole, produces an increase in the Cmax of THC, its main metabolite, and CBD. Therefore, if treatment with this type of inhibitor is initiated, dose adjustment may be necessary. In addition,

concomitant treatments with CYP3A4 inducers such as rifampicin reduce the Cmax and ABC of THC, its main metabolite, and CBD, so this concomitant therapy should be avoided (GW PHARMACEUTICALS, 2016). Other important interactions to be considered in this context are benzodiazepines and valproic acid due to increased sedation and hepatic transaminases (ABRAMOVICI, 2018).

Other possible side effects of cannabis (high in THC) include panic attacks or anxiety. It should be noted that, contrary to the usual belief, psychiatric disorders can be exacerbated if they are already present, but very rarely are they induced by cannabis use. It can also have cardiovascular effects that include increased heart rate (by 20 to 50%, which can last from a few minutes to three hours), increased blood pressure, and orthostatic hypotension (JOHNS, 2001).

A clinical program of Sativex®, which included 1500 participants with multiple sclerosis, in placebo-controlled trials and in long-term open-label studies, adverse reactions classified according to frequency were reported. As for metabolic disorders, we often have anorexia and increased appetite. Regarding psychiatric disorders, depression, disorientation, dissociation, euphoric mood are frequent and hallucinations, illusions, paranoia, suicidal ideation, delusional perception are uncommon. As for nervous system disorders, dizziness is very frequent, followed by amnesia, impaired balance, impaired attention, dysarthria, dysgeusia, lethargy, impaired memory, drowsiness and less syncope less frequently (GW PHARMACEUTICAL, 2016). In addition, blurred vision and vertigo are also frequent changes. In the cardiac and vascular system, participants infrequently presented palpitations, tachycardia and hypertension. When it comes to respiratory disorders, throat irritation was also seen infrequently. As for gastrointestinal issues, constipation, diarrhea, dry mouth, ulceration of the oral mucosa, nausea, discomfort in the mouth, oral pain, vomiting and less frequently: abdominal pain (upper), change in the color of the oral mucosa, oral alteration, exfoliation of the oral mucosa, stomatitis, discoloration of teeth. In addition to these, fatigue was reported very frequently, pain in the application area, asthenia, abnormal sensation, feeling of intoxication, malaise were frequent and irritation in the application area was presented as uncommon. All adverse events listed were considered “mild” (GW PHARMACEUTICAL, 2016).

As for patients with neurosurgery-related diseases, patients with pathologies such as neoplasms (triggering seizures/Epilepsy) have the benefit of controlling the aforementioned clinical manifestations as well as beneficial effects on pro-inflammatory

actions in the Central Nervous System (CNS). See the summary and discussion of the case report below:

It is known that the treatment of some CNS tumors, particularly the malignant ones, is still not enough to allow the patient to remit the disease and improve survival (11). The total surgical resection of the tumor can contribute to improve the clinical picture, allowing, for example, the control of convulsive crises and intracranial hypertension (20). On the other hand, in certain cases, tumor recurrences are very common. Astrocytomas often recur at the margins, even after complete resection (20, 21).

Shaw et al., 2008 reported the results of a phase II trial of observation of 11 young adults undergoing neurosurgical-determined extensive resection (22). In this study, participants were closely monitored, performing MRI every six months and demonstrated a risk greater than 50% of postoperative tumor progression, alerting to the need for surveillance, as well as the importance of adjuvant therapies (22). In view of this, the literature brings studies, demonstrating, in addition to the treatment considered gold standard, whether total resection surgery or associated with adjuvant radiochemotherapy, the possibility of including cannabinoids in treatments, with the function of attenuating proliferation, angiogenesis and inducing apoptosis in several tumor types, including high-grade tumors such as anaplastic astrocytoma and glioblastoma (12, 13).

This treatment with cannabinoids would be based on the interaction of cannabinoids with the receptors (CB1 and CB2) being present in some neurological tumors, thus leading to the suppression of the activity of the Akt molecular pathway, exhibiting antitumor action (14). In this context, it is clear that several events and signal transduction pathways triggered by the stimulation of CB1 and CB2 receptors have already been described as participating in cannabinoid-induced cell death in various tumor cells (15-17). For the patient in the present case, the neurosurgical evaluation determined the drainage and total excision of the intracranial cystic lesion with adjuvant chemoradiotherapy. Therefore, the introduction of CBD:THC oil at a 1:1 concentration occurred after tumor resection as an adjuvant treatment, allowing a possible antitumor benefit, considering the risk of recurrence.

According to the results of randomized clinical trials in the literature, it was observed that the patient in the present study, using THC:CBD Oil (1:1), had a reduction in the frequency of seizures, reinforcing studies that advocate the significant

role of cannabinoids in treatment of refractory epilepsies (18,23). Agonist activity at CB1 and CB2 endocannabinoid receptors demonstrated anticonvulsant effects seen with THC, however CBD shows low affinity and negative allosteric effects on them (29). Its antiepileptic mechanism is not yet well established, but CBD has been shown to block the absorption and hydrolysis of anandamide, effectively increasing its availability to activate CB1 and CB2 receptors so that it can modulate the activation of these receptors indirectly (24). Another possible mechanism is the activation of the transient receptor potential (TRP) of vanilloid type 1 (TRPV1), which is also an anandamide receptor and can modulate calcium channels (24).

Furthermore, with the use of CBD oil: THC (1:1), the patient obtained effective gains in cognitive, social and behavioral interaction, which resulted in a positive impact on the prognosis and quality of life of the individual. There is evidence of possible cognitive and behavioral gains associated with CBD use (25,27). The patient in this study showed a significant gain in attention/interaction with the environment as well as socialization; the intrinsic limitations of the individual are highlighted (given their clinical history). During the evolution and improvement, after neurosurgery and hospital discharge, with the use of CBD/THC 1:1 oil, better interaction between the patient and their families was noticed - language and attention to the environment. The pattern of irritability episodes in the study patient, in terms of frequency and duration, was attenuated after using the oil, and the beneficial action of cannabinoids on cognition and behavior has already been demonstrated in studies (25-28).

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