Cannabidiol in Canine Drug-Resistant Epilepsy. A Comprehensive Case Study of Jack's Journey

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Case Report

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CANNABIDIOL IN CANINE DRUG-RESISTANT EPILEPSY

A Comprehensive Case Study of Jack's Journey

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Abstract

This paper presents a detailed case study of Jack, a canine diagnosed with drug-resistant epilepsy, focusing on the effectiveness of Cannabidiol (CBD) monotherapy as a treatment strategy. Jack exhibited resistance to conventional antiepileptic drugs such as phenobarbital and potassium bromide, prompting the exploration of alternative therapeutic approaches. The study analyzes Jack's response to CBD administration, dosage adjustments, and its long-term impact on epilepsy management. It also examines potential interactions with the cytochrome P450 enzyme system and the neuroprotective properties of CBD.

Key findings suggest that CBD effectively controlled seizure activity in this case, highlighting its potential role as a primary therapeutic option in selected patients. This case study contributes to the growing body of evidence supporting CBD as a viable therapeutic option in the management of refractory canine epilepsy.

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1 – Case Description

Name: *Jack.*
Species: *Canine.*
Breed: *Belgian Malinois Shepherd x Basque Shepherd. (Belgian Malinois dominant traits)*
Gender: *Male.*
Life Expectancy: *12-14 years.*
Date and place of birth: *4/12/2010, Basque Country, Spain.*
Date of First Epilepsy Episode: *29/04/2016 (age: 5 years, 5 months)*
Date of Last Epilepsy Episode: *01/09/2018 (age: 7 years, 9 months)*
Age at study: *15 years, 1 month.*

Jack, a crossbreed of Belgian Malinois Shepherd and Basque Shepherd, was rescued in March 2012 from a local kennel. At the age of 5, he experienced his first epileptic seizure, leading to a diagnosis of idiopathic canine epilepsy. Conventional antiepileptic drugs failed to control his severe, drug-resistant epilepsy, resulting in a decline in overall health and quality of life.

2 – Introduction: Canine Epilepsy

Approximately 1% of the human population suffers from epilepsy *(1)*. Due to the substantial similarity of the central nervous system among mammals, this condition also occurs in other species with a similar incidence and prognosis. In dogs, epilepsy affects around 0.6-0.75% of the population *(2,3)*, rising to over 9,5% in Belgian Shepherds *(4,5)*. The first symptoms typically appear around 3 years of age, usually between 6 months and 6 years. Later onset may indicate an underlying condition, such as a brain tumor, which can produce similar symptoms *(6)*.

Epilepsy is defined as a disease of the brain characterized by an enduring predisposition to generate epileptic seizures. This definition is usually practically applied as having at least two unprovoked epileptic seizures >24 hours apart *(7)*. Epilepsy occurs when a group of neurons in a specific brain area exhibits excessive electrical activity for a short period (seizure), returning to normal between episodes. Seizures can be focal—causing tremors, spasms, or loss of control in part of the body without loss of consciousness—or generalized, involving loss of consciousness and full-body motor symptoms, including rigidity, convulsions, jaw spasms, and loss of sphincter control.

Before a seizure, a prodrome or aura may occur, lasting from a few minutes up to 48 hours, during which the patient may show agitation, nervousness, or unusual behaviors. After a seizure, the post-ictal phase involves regaining consciousness, body control, and normal breathing and heart rate, though disorientation, exhaustion, and temporary sensory impairment are common.

If more than two seizures occur within 24 hours, the patient is experiencing cluster seizures, which may progress to Status Epilepticus (SE) if a seizure lasts over 5 minutes or two discrete seizures occur without full recovery between them. SE is a medical emergency, potentially life-threatening, requiring hospitalization and close monitoring. Cluster seizures and SE can lead to permanent brain damage, heart failure, coma, or death *(8)*.

Seizures caused by an underlying intracranial pathology are termed Structural Epilepsy, including conditions such as meningitis, cancer, trauma, vascular disorders, or viruses capable of crossing the blood-brain barrier. Seizures arising from external or systemic causes are labeled Reactive Epilepsy, triggered by toxins, metabolic imbalances (e.g., hypoglycemia), or organ dysfunction (liver, kidney, etc.).

Diagnostic tests to identify the primary cause include complete blood analysis (including liver function), MRI of the brain, and cerebrospinal fluid analysis. If all results are negative, the diagnosis is Idiopathic Epilepsy, often with a strong genetic component; some studies link it to a mutation on homozygous Chromosome 37 in Belgian Shepherds *(5)*.

Epilepsy is chronic and progressive. Treatment aims to control seizures and maintain quality of life. When managed, an episode every three months is considered reasonable. Seizure frequency may increase with age, and the condition is associated with premature brain and central nervous system aging.

3 – Primary Treatment: Conventional Veterinary Drugs

The initial veterinary treatment for canine epilepsy involves two categories of drugs: maintenance drugs and emergency drugs. Maintenance drugs are administered daily to control seizures over the long term. They may be given as monotherapy (a single drug) or polytherapy (a combination of drugs) to achieve optimal seizure control. While some primary drugs are effective in the majority of patients, certain individuals may require a personalized combination of drugs. Determining the most effective therapy often involves a careful trial-and-error process, taking into account both drug selection and dosage. Emergency drugs, on the other hand, are administered during acute seizure episodes with the goal of halting the seizure and minimizing potential harm. Their use is particularly critical in cases of seizure clusters or Status Epilepticus, where rapid intervention is essential to protect the patient's health.

3.1 – Maintenance Drugs

This section reviews the maintenance drugs administered to Jack for long-term control of his epilepsy. Only the medications actually used in his treatment are discussed, with attention to their mechanisms of action, dosages, and possible side effects.

3.1.1 – Phenobarbital

Phenobarbital (PHB) is a barbiturate drug commonly chosen as the first-line treatment for epilepsy. It aids in reducing and controlling seizures by increasing the inhibitory effects of the neurotransmitter gamma-aminobutyric acid (GABA) at GABA-A receptors *(9, 10)*. With a high oral or intramuscular (IM) bioavailability of 80-100%, it is widely used in veterinary medicine *(11)*.

Mechanism of action: The primary action of phenobarbital is to enhance the inhibitory effects of GABA on neurons by binding to the barbiturate-binding site, prolonging the duration of chloride channel opening. Simultaneously, sodium and potassium cations conductance and calcium influx are reduced, and glutamate excitability is depressed. This elevates the seizure threshold, making it more difficult for a crisis to be triggered and reducing the spread of seizure activity from a seizure focus.

Dosage: For epilepsy treatment, the dosage is typically set between 2-6 mg/kg/day, with adjustments made for each patient by analyzing serum concentrations until stabilization occurs between 15 – 35 µg/mL *(12)*. Oral administration is usually prescribed every 12 hours. A loading dosage is often required at the beginning of treatment, consisting of an intake of up to three times the standard dosage during the first 48 hours *(13)*.

Metabolism and half-life: Phenobarbital is metabolized through the liver by the hepatic Cytochrome P450 system and excreted renally. It is rapidly and nearly completely absorbed following oral and intramuscular administration, with peak serum concentrations reached in approximately 3 hours. The half-life ranges between 80 and 100 hours *(14, 15)*, making it a stable drug choice. Daily doses and plasma concentrations exhibit a linear relationship.

Side effects: Polyuria / polydipsia, polyphagia, depression, hyperactivity, impaired attention, dizziness, memory problems, loss of strength and control of the posterior train (ataxia), liver failure, and superficial necrolytic dermatitis.

The majority of these side effects can be reversed upon discontinuation of the drug.

3.1.2 – Potassium Bromide

Potassium bromide (KBr) is a halide anticonvulsant often administered in combination with other first-choice drugs, although it can also be used in monotherapy . Upon ingestion, the salt dissociates and the bromide ion is rapidly absorbed, reaching peak serum concentration after only 30 to 45 minutes from oral administration *(16)*. Once absorbed, bromide quickly distributes throughout the extracellular space and into cells, replacing chloride in all body fluids. Achieving and maintaining this balance can be complex and is susceptible to disruption by external factors such as diet, water intake, or physical activity.

Mechanism of action: Potassium bromide's anti-epileptic activity stems from the competition between bromide and chloride for transport across nerve cell membranes. This results in membrane hyperpolarization, raising the seizure threshold and preventing the spread of epileptic discharges *(17)*. Bromide also potentiates the effects of the inhibitory neurotransmitter GABA, exhibiting synergistic activity with other drugs that have GABA-ergic properties, such as phenobarbital *(18)*. This is why it is often part of a polytherapy when the first-choice drug is not effective.

Dosage: The target therapeutic range for bromide in serum concentration is typically between 1000-1500 µg/mL, achieved through oral administration of 20-40 mg/kg/day *(19)*. It can take around a month to reach a steady state of bromide concentration in the patient's body. External influences, such as the intake of common salt (NaCl), can impact bromide concentration.

Metabolism and half-life: Potassium bromide is not metabolized; it is excreted by the renal system. The half-life ranges between 25-46 days *(20,21)*.

Side effects: Polyuria / polydipsia, polyphagia, nausea, vomiting, drowsiness, ataxia, and erythematous dermatitis.

The majority of these side effects can be reversed upon discontinuation of the drug.

3.2 – Emergency Drugs

Emergency drugs are not part of daily epilepsy management and are used only during active seizures, especially in cluster seizures or Status Epilepticus. Their role is to stop the seizure quickly and reduce the risk of damage or complications *(22)*. The following section describes only the emergency drugs that were used in Jack's treatment.

3.2.1 – Diazepam

Diazepam (D) is a benzodiazepine drug with anxiolytic, hypnotic, anticonvulsant, muscle relaxant, and amnesic effects. It acts by calming abnormal overactivity in the brain and is particularly used as an emergency drug to halt cluster seizures. Typically, it is administered rectally during a crisis, although it can also be given as a continuous intravenous infusion after hospitalization *(23)*.

Mechanism of action: The presumed mechanism of action of diazepam and other benzodiazepines in the central nervous system involves potentiating the inhibitory effect of GABA on neuronal transmission *(24, 25)*.

Dosage: Diazepam is commonly administered as a rectal gel during emergencies. The emergency dosage is typically 0.5-2 mg/kg, which can be repeated up to three times at intervals of 5-10 minutes *(25)*. Peak concentration is expected within 5-10 minutes of rectal administration. Exceeding the recommended dosage may lead to the opposite effect, provoking overexcitement and seizures *(26)*.

Metabolism and half-life: Diazepam is metabolized in the liver by hepatic isoenzymes CYP2C19 and CYP3A4 and the Cytochrome P450 system, with a half-life of approximately 3 hours *(27)*.

Side effects: Drowsiness, dizziness, headache, nervousness, flushing, diarrhea, unsteadiness, lack of coordination, problems falling asleep or staying asleep, rash, trouble breathing, and overexcitement.

3.2.2 – Levetiracetam

Levetiracetam (LEV) belongs to the pyrrolidine class and is used to treat various types of seizures in epileptic disorders. It has a wide therapeutic index and minimal potential for pharmacokinetic interactions. Levetiracetam can theoretically serve as a maintenance drug due to its relatively long half-life *(28)*, near the lower limit for stable daily concentrations. In practice, it is more commonly used as an emergency medication during acute epileptic episodes.

Mechanism of action: Levetiracetam is rapidly and nearly completely absorbed after oral administration. Peak serum concentrations are reached within 1-2 hours. Daily doses and plasma concentrations are linearly related. The unique mechanism through which levetiracetam exerts its antiepileptic effect involves binding to synaptic vesicle protein 2A (SV2A) (29, 30). This protein plays a role in modulating synaptic transmission by increasing the available amount of secretory vesicles for neurotransmission. Levetiracetam's stimulation of pre-synaptic SV2A may inhibit neurotransmitter release without affecting normal neurotransmission. It also indirectly affects GABAergic neurotransmission and modulates ionic currents.

Dosage: A loading dose of 60mg/kg is required, followed by a regular dosage of 20-30 mg/kg every 8 hours due to its half-life *(31)*.

Metabolism and half-life: Levetiracetam has a half-life of approximately 6-8 hours and is metabolized renally. It is not protein-bound (<10%) and has no association with hepatic metabolism via the Cytochrome P450 system. The major metabolic pathway involves the hydrolysis of the acetamide group to the inactive carboxylic derivative *(31)*.

Side effects: Polyuria / polydipsia, polyphagia, weakness, lethargy, somnolence, and loss of coordination and balance.

4 – Cannabidiol (CBD)

Cannabidiol (CBD) is one of the multiple cannabinoids present in the cannabis plant, second only to the more well-known THC. Unlike THC, CBD is non-psychoactive. In epilepsy treatment, CBD is often administered as a complementary drug to the primary medical treatment. Although much is still unknown about CBD's properties and mechanism of action, various tests and studies suggest its potential efficacy against symptoms related to different illnesses and conditions such as muscular pain, inflammatory-related aches, CNS affections like multiple sclerosis, fibromyalgia, epilepsy, glaucoma, and some skin disorders. CBD is also believed to have neuroprotective properties, with ongoing studies for Parkinson's and Alzheimer's diseases *(32,33,34)*.

Mechanism of action: The exact mechanism of action of CBD against epilepsy is under study, with preliminary tests suggesting several possible ways CBD may work:

- Inhibiting or slowing down the transmission of messages or signals in the brain by changing calcium levels in brain cells *(35, 36)*.
- Potentiating the inhibitory effect of GABA on glutamatergic neuronal groups *(37, 38)*.
- Exerting anti-inflammatory properties, relieving areas of the brain affected by epilepsy and potentially masking the principal sickness by decreasing the inflammatory process causing seizures.
- Potentially inhibiting the Cytochrome P450 enzymes system *(39, 40)*, specifically CYP2C9, affecting the metabolization of other drugs used in polytherapy. As a consequence of this inhibition, the biodisponibility and serum concentration of the primary antiepileptic drug may be artificially increased. This increase in drug concentration can result in a more potent effect and better control of epileptic crises. However, it concurrently elevates the risk of hepatoxicity *(41)*, as the liver is responsible for metabolizing these drugs. The intricate interplay of multiple drugs in polytherapy, combined with the impact of CBD on the enzymatic system, requires careful consideration and monitoring. Detailed exploration of this specific interaction is provided in *Chapter 5.4* of the present document.

Dosage: The dosage of Cannabidiol can vary depending on the patient, and it is subject to individual response and the specific condition being treated. For humans, the typical dosage range is from 0.5 to 10 mg/kg/day. There have been documented cases where higher dosages, up to 50 mg/kg/day *(42)*, have

been used without reporting any signs of toxicity. In veterinary patients, the study dosage is currently set at 2.5 mg/kg every 12 hours *(43)*. This dosage is based on ongoing research and is tailored to the specific needs and responses of animals.

An important consideration in cannabinoid therapy is the concept of the Entourage Effect. This phenomenon suggests that the presence of multiple cannabinoids, even those not specifically targeted at a particular sickness or condition, can enhance the effectiveness of the main cannabinoid, in this case, CBD *(48, 49)*. This implies that a lower amount of the primary cannabinoid may achieve the same theoretical effectiveness when combined with other cannabinoids. Understanding the Entourage Effect underscores the significance of using full-spectrum or broad-spectrum CBD products, which contain a range of cannabinoids, terpenes, and other beneficial compounds naturally present in the cannabis plant.

Metabolism and half-life: Cannabidiol undergoes metabolization primarily in the liver through the Cytochrome P450 enzyme family, involving various isoforms such as CYP2B6, CYP2C19, CYP2D6, CYP2J2, and CYP3A4. Additionally, it is metabolized by the isoenzymes UGT1A7, UGT1A9, and UGT2B7 *(40)*. This extensive involvement of different enzymes contributes to the complex metabolic pathway of CBD.

During the process of first-pass metabolism, which occurs after CBD passes through the liver, a significant portion of the compound is eliminated, leading to the formation of numerous metabolites. Some examples of these metabolites include 7-COOH-CBD and 7-OH-CBD. The sheer diversity of more than 100 identified metabolites adds to the challenge of understanding which specific metabolites are responsible for particular effects.

The half-life of CBD after chronic oral administration is reported to be in the range of 2–5 days *(44)*. This extended half-life indicates that CBD remains in the system for a considerable duration, contributing to its significant biodisponibility and stability.

Side effects: Cannabidiol is generally considered a safe drug based on several tests, even at relatively high dosages. No serious side effects have been detected thus far in clinical studies. These side effects are typically temporary and may diminish over time as the body adjusts to the treatment. Commonly reported mild side effects include: Gastric discomfort, nausea, headache, drowsiness (particularly during the initial stages), and lethargy (particularly during the initial stages).

It's essential to highlight that these side effects are typically considered minor and temporary. However, individual responses may vary, and some individuals may be more sensitive to CBD than others. Additionally, there is limited research on the long-term side effects of CBD for chronic patients, so ongoing monitoring and further investigation are important *(45, 46, 47)*.

5 – CBD treatment for a Case of Canine Epilepsy – Jack

This chapter introduces Jack's journey with drug-resistant epilepsy and the rationale behind exploring cannabidiol (CBD) as a therapeutic option. It outlines the context of his condition, previous treatments, and the challenges faced before CBD was considered. The following sections detail the selection of the CBD product, the administration protocol, clinical observations over time, and the subsequent pharmacological analysis of interactions with conventional medication.

5.1 – Case Introduction and Background

Jack's journey with canine epilepsy began on April 29th, 2016, when he experienced his first isolated epilepsy crisis. Following this, another isolated crisis occurred a month later, and in June of the same year, Jack faced his first epilepsy crisis in cluster. Subsequently, the administration of phenobarbital, a first-choice antiepileptic drug, commenced.

By August 2016, extensive diagnostic tests, including blood tests, MRI scans, and Cerebrospinal Fluid analyses, were conducted to eliminate potential primary diseases responsible for both secondary and reactive epilepsy. The results of these tests did not reveal any underlying causes, leading to the diagnosis of Idiopathic Epilepsy in Jack.

After Jack's diagnosis of Idiopathic Epilepsy and the initiation of phenobarbital monotherapy, his condition was relatively stable for around 10 months, with seizures occurring every 4 to 8 weeks. However, in early 2017, the frequency of seizures increased significantly, happening every 2 weeks or less, and they started to manifest in clusters, sometimes leading to Status Epilepticus.

The routine during this period involved the regular administration of phenobarbital alongside emergency drugs, such as diazepam and levetiracetam. The side effects of these emergency drugs were notable, including disorientation, loss of urinary control, and lethargy. This pattern became a recurring part of Jack's life, with some days spent in a post-ictal state, followed by an aura indicating the impending next cluster of seizures.

During this period, Jack exhibited a highly recurrent and predictable two-week seizure pattern. Cluster seizures consistently occurred on day 0 (baseline), often persisting throughout the day. Initial emergency intervention with diazepam was frequently ineffective, necessitating subsequent administration of levetiracetam.

From days 0 to 5, levetiracetam was administered three times daily as a full emergency course. This phase was associated with pronounced adverse effects, including severe disorientation, loss of urinary control, marked ataxia, and profound lethargy, during which Jack remained largely immobile and asleep for most of the day.

Day 6 typically represented a transition period following discontinuation of emergency medication. From days 7 to 10, Jack experienced a relatively stable interval, characterized by an absence of seizures and no requirement for emergency interventions.

Between days 11 and 12, a prodromal phase was consistently observed, marked by behavioral and neurological changes suggestive of an aura, including nervousness, irritability, and intense nightmares. On day 13, a new episode of cluster seizures occurred, effectively resetting the cycle.

In May 2017, due to the worsening situation and the failure of phenobarbital monotherapy, a second antiepileptic drug, potassium bromide (KBr) was introduced in polytherapy. While this combination initially showed success in preventing seizures for the next two months, Jack experienced serious side effects, including severe skin reactions, hair loss, paralysis, episodes of spontaneous pain, tremors, and irritability. As a result of these side effects and the resumption of seizures, potassium bromide was discontinued, and Jack returned to phenobarbital monotherapy. The seizures, however, returned at their

previous frequency, and euthanasia became a consideration. At this critical juncture, CBD emerged as a potential treatment option.

Inspired by the positive outcomes observed in a young girl with Dravet syndrome, Charlotte Figi*, who responded well to a high cannabidiol strain of marijuana, CBD oil was chosen as a last-resort treatment for Jack's epilepsy. The CBD oil was administered in combination with the primary antiepileptic drug, phenobarbital, initially in a polytherapy approach.

The introduction of CBD oil marked a crucial turning point in Jack's treatment journey, offering a glimmer of hope when other options had faltered. The subsequent sections will delve into the details of Jack's response to CBD treatment and the broader implications for managing canine epilepsy.

5.2 – Cannabidiol oil: Product Characteristics and Selection

When selecting a cannabidiol extract oil for Jack's treatment, certain specifications were deemed crucial for effectiveness and safety. The chosen CBD oil needed to meet the following criteria:

- High CBD concentration: A higher concentration ensures the administration of an adequate dose with a reasonable volume of oil.
- Full cannabinoid spectrum: This promotes the entourage effect *(48, 49)*, where various cannabinoids work synergistically to enhance CBD's efficacy.
- Very low THC content: To prevent psychoactivity and avoid the potential emergence of THC-related epilepsy crises *(50)*.
- Decarboxylated product: The cannabidiol molecule should be already activated for optimal oral administration.
- Reliability: Certification from different third-party laboratories attesting to product quality, stability, safety, and absence of heavy metals through chemical and spectrometry tests.

Based on the previously defined criteria, a commercially available full-spectrum cannabidiol oil (Enecta Premium Hemp Extract, 10% CBD) was selected. The 10% concentration allowed accurate dosing while keeping the administered oil volume within practical limits.

5.3 – Cannabidiol Treatment and Results

CBD administration commenced on October 18th, 2017, at a very low dosage of 0.6 mg/kg/day, given twice daily, in conjunction with phenobarbital (PHB). The primary drug, PHB, was being administered at the maximum tolerable dosage for Jack, 250 mg/day, while potassium bromide had already been fully discontinued due to previous adverse effects.

Jack remained mostly inactive for the first two days following the introduction of CBD; by day three, his activity appeared normal. After one week, the CBD dosage was increased to 1 mg/kg/day. The subsequent cluster seizure occurred approximately two weeks later, showing no change in frequency or severity, and emergency drugs were required to halt the episode.

The CBD dosage was then increased to 1.2 mg/kg/day. The following cluster seizure occurred two weeks and four days later, again with no substantial change in frequency or intensity. On one occasion, a single high-dose oral administration of CBD (60 mg) was attempted as an emergency intervention, but it proved ineffective, and conventional emergency drugs were administered as usual.

Subsequently, the CBD dosage was raised to 2 mg/kg/day. Jack remained mostly inactive for two days, resuming normal activity on the third day. After four weeks without seizures, it became apparent that cannabidiol was contributing to seizure control. To determine the precise role of CBD, PHB was gradually reduced while maintaining a constant CBD dosage of 2 mg/kg/day.

Initially, PHB was lowered to 200 mg/day. After four weeks, Jack remained seizure-free. The dosage was then reduced to 150 mg/day, and after eleven more weeks, no seizures were observed. PHB was further lowered to 100 mg/day, at which point Jack exhibited improved strength and coordination in the hind limbs, along with marked reductions in hair loss, polyuria, and polyphagia.

After a total of 29 weeks without seizures, PHB was reduced to 50 mg/day. Serum tests indicated PHB levels below the therapeutic range, suggesting that cannabidiol was primarily responsible for the observed improvements. PHB-related side effects had completely disappeared, while CBD dosage remained at 60 mg/day (2 mg/kg/day).

On August 22nd, 2018, PHB was again reduced to 25 mg/day. On September 1st, nine months and five days after the last cluster seizure, Jack experienced a single moderate-intensity seizure and recovered rapidly without the need for emergency medication. To stabilize treatment, PHB was temporarily restored to 50 mg/day, establishing a stable polytherapy regimen of 60 mg/day CBD plus 50 mg/day PHB, representing only 20% of the initial PHB dosage.

Throughout 2019, Jack remained seizure-free. CBD dosage continued at 2 mg/kg/day, while PHB was progressively decreased, reaching 25 mg/day (10% of the initial dosage) by early 2020, with the goal of complete PHB discontinuation. In February 2020, serum tests confirmed PHB levels below half the minimum therapeutic range, while CBD dosage remained at 60 mg/day. On May 26th, 2020, PHB was fully discontinued after a gradual tapering period. Since then, Jack has been maintained on CBD monotherapy, showing no seizures, no side effects, and high activity levels. The last seizure occurred over seven years ago, and no adjustment of CBD dosage has been necessary since November 27th, 2017.

5.4 – Study of CBD Interactions: Cytochrome P450 and Phenobarbital

Cannabidiol (CBD), like many drugs, can potentially interact with other molecules and influence metabolic processes. Specifically, studies have cautioned about the possible inhibition of Cytochrome P450 enzymes *(39, 40)*, which play a key role in the metabolism of numerous substances in the liver, including barbiturates such as PHB. Inhibition of these enzymes could theoretically slow down PHB metabolism, resulting in higher serum concentrations for the same administered dose.

Given the clear improvement in Jack’s epilepsy with the combined use of CBD and PHB, a critical question emerged: is CBD acting directly as the primary antiepileptic agent, or indirectly by increasing PHB bioavailability? Two scenarios were considered. In the first, CBD directly reduces seizures through

neural mechanisms. In the second, CBD inhibits Cytochrome P450, which increases serum PHB concentrations and indirectly contributes to seizure reduction.

To investigate this, PHB dosage for Jack was gradually reduced while maintaining a constant CBD dosage of 2 mg/kg/day. Serum PHB concentrations were measured after each stabilization period (minimum two weeks per dosage step) to monitor potential interactions.

The first step compared PHB serum concentrations before CBD administration with those during combined PHB + CBD therapy, using the same daily PHB dose. The results are summarized in *Table 1*:

PHARMACOTHERAPY	PHB MONOTHERAPY	PHB + CBD POLYTHERAPY
DATE	25/08/2017	23/01/2018
PHB DOSAGE (mg/day)	200	200
[PHB] SERUM (µg/ml)	26.2	26.5

Table 1: PhB serum concentrations in PHB monotherapy and PHB + CBD politherapy.

As shown, serum concentrations at 200 mg/day were virtually identical between monotherapy and polytherapy, suggesting no significant effect of CBD on PHB metabolism at this dosage.

The second step examined PHB serum concentrations at various doses during the gradual de-escalation, keeping the CBD dosage constant. The data are presented in *Table 2* and *Figure 1*:

PHB DAILY INTAKE (mg)	WEIGHT (Kg)	PHB DOSAGE (mg/Kg/day)	SERUM [PHB] (ug/ml)		
			MIN (VALLEY)	MAX (PEAK)	AVE
250	30	8.33	34.1	36.7	35.4
200	30	6.67	26.2	26.2	26.2
200	29	6.9	26.5	26.5	26.5
50	29	1.72	12	12	12

Table 2: PhB serum concentrations at different PHB dosages on PHB + CBD politherapy data.

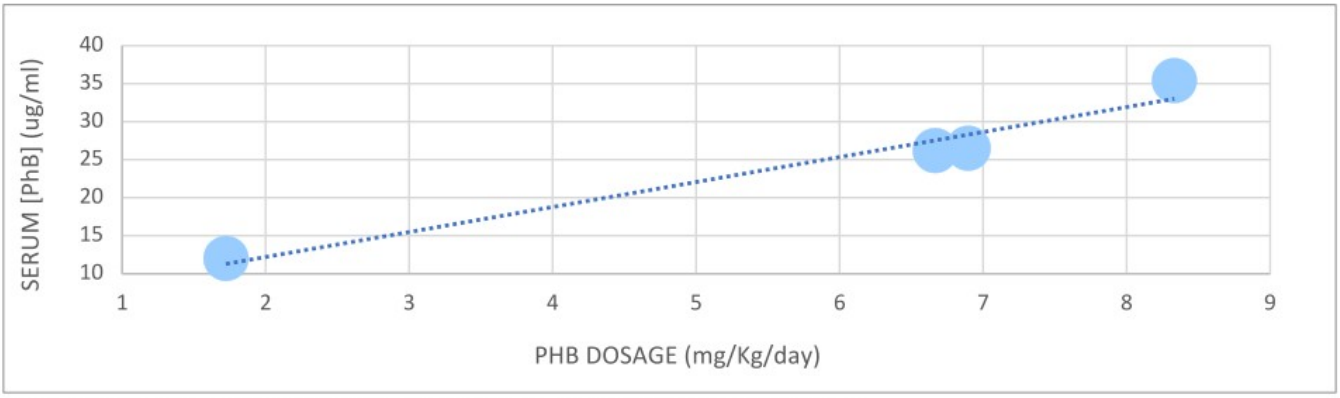

Figure 1: PHB serum concentrations at different PHB dosages on PHB + CBD politherapy.

Despite the significant limitations of this regression study, a clear linear trend is observed between PHB dose reduction and serum PHB concentration. Importantly, the absence of a pronounced hyperbolic curve, which would be expected if Cytochrome P450 inhibition occurred, indicates that CBD does not interfere with PHB metabolism at the administered dosages.

Taken together, these observations strongly suggest that CBD acts directly as the primary agent in controlling Jack's epilepsy, rather than indirectly by altering PHB bioavailability.

6 – Summary and Conclusions.

Effectiveness of CBD Monotherapy: As of the time of writing, Jack has been free from epilepsy crises for over seven years since 01/09/2018. This prolonged seizure-free period strongly supports the conclusion that CBD monotherapy has been effective in managing Jack's epilepsy.

Optimal Dosage: Jack currently receives a daily CBD dosage of 60 mg (2 mg/kg/day). Compared to ongoing research and reported dosage ranges for epilepsy treatment (0.5–10 mg/kg/day), this dosage is relatively low.

Genetic Cause: Jack's epilepsy is diagnosed as Idiopathic Epilepsy, suggesting a likely genetic origin, particularly considering the Belgian Malinois lineage in his crossbreed.

Traditional Drug Effectiveness: Jack is refractory to both phenobarbital and potassium bromide, commonly used antiepileptic drugs. Additionally, diazepam proved ineffective as an emergency drug, and tolerance to levetiracetam was poor.

Non-Inhibition of Cytochrome P450: The study confirms that CBD, at the administered dosage, does not inhibit Cytochrome P450.

No drug tolerance effect: Jack has shown no tolerance to CBD over eight years of continuous intake, and there has been no need for a dosage increase after the initial effective dose.

Neuroprotective Effect: Jack has shown no cognitive decline despite his age and medical history, suggesting a potential neuroprotective effect of CBD. This contrasts with typical neurodegenerative progression observed in epilepsy, indicating a positive impact on cognitive function.

Potential Long-Term and neuroregenerative effectiveness: The observation that CBD might enhance its effectiveness over time is notable. The incident where a crisis occurred upon reducing Phenobarbital dosage, followed by a subsequent reduction without crises a year later, suggests a potential long-term impact of CBD on the neuronal system. This aligns with existing studies highlighting CBD's neuroregenerative properties *(51)*.

Ineffectiveness of CBD as an Emergency Drug: CBD has shown no immediate effect when used as an emergency drug in this case. This indicates that CBD's beneficial effects are gradual rather than providing fast seizure control.

Loading Period: A loading period of several days (2–7 days) was observed during the initial administration or dosage increases. During this period, Jack typically slept extensively for 2–3 days

before returning to normal mental and physical activity, indicating an adjustment phase for CBD in the system.

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-Jack*: For the insane bond we have built together over this journey. Your unwavering spirit and resilience are an inspiration every day.*

*In loving memory of Charlotte Figi (October 8, 2006 – April 7, 2020) and her brave family, whose story changed ours.

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