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Real-world evidence on the use of cannabidiol for the treatment of drug resistant epilepsy not related to Lennox-Gastaut syndrome, Dravet syndrome or Tuberous Sclerosis Complex

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ABSTRACT

Introduction: Highly purified cannabidiol (CBD) has a broad spectrum of action and could be useful for the treatment of drug resistant epilepsy regardless of etiology or syndrome.
Materials and methods: Multicenter retrospective study that evaluated the efficacy and safety of CBD for the treatment of drug resistant epilepsy of different etiologies in patients >2 years of age.
Results: Seventy-eight patients with a median age of 24 years and a wide spectrum of mainly structural and genetic etiologies were included. Patients were using a median of 3 antiseizure drugs (IQR=2–4) and had a median of 30 monthly seizures (IQR=12–100) before starting CBD. The median treatment time with CBD was 14 months (IQR=10–17). The efficacy analysis at the last available visit showed that mean percent reduction in seizures, ≥50% reduction in seizure frequency and seizure freedom was 67.8%, 68.8% and 11.5% respectively. We found no significant impact of concomitant clobazam use on the efficacy and safety of CBD. In the safety analysis, 28.2% ($n = 22$) of patients presented adverse events related to CBD and drug-retention rate was 78.2%.
Conclusions: In a real-world setting, highly purified CBD has been shown to be safe and effective for the treatment of drug resistant epilepsy not related to Lennox-Gastaut syndrome, Dravet syndrome or Tuberous Sclerosis Complex. Based on these findings, highly purified CBD should be considered as an adjuvant therapy for drug resistant epilepsy, regardless of its underlying cause or specific syndrome. Nevertheless, this assumption should be validated through further controlled trials.

1. Introduction

Highly purified cannabidiol (CBD) with a known and constant composition has proven to be an effective and safe therapeutic alternative for the treatment of drug resistant epilepsy [1,2]. The results of several randomized controlled clinical trials have allowed it to be approved by various drug regulatory entities as adjuvant therapy in patients older than 2 years with drug resistant epilepsy associated with Lennox-Gastaut syndrome, Dravet syndrome or Tuberous Sclerosis Complex [3–7]. However, the mechanism of action of CBD in epilepsy, although not fully described, is multifactorial and is not exclusively related to the pathophysiology of these epileptic syndromes [8]. Some studies have shown that CBD modulates the neuronal calcium mobilization and influx via G protein-coupled receptor-55 (GPR55) and Transient receptor potential vanilloid-1 (TRPV1) respectively [9,10]. It could also be implied in adenosine signaling through the modulation of equilibrative nucleoside transporter-1 (ENT-1) [11]. All of these hypothesized mechanisms of action suggest that CBD has a broad spectrum of action related to a multifactorial modulation of neuronal hyperexcitability and therefore could be useful for the treatment of epilepsy regardless of etiology or syndrome. Some recent studies have supported that assumption [12–16]. For all these reasons, we decided to perform a

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multicenter retrospective study in a real-world setting to evaluate the effectiveness and tolerability of a highly purified, plant-derived CBD oil-based solution in patients with drug resistant epilepsy not related to Lennox-Gastaut syndrome, Dravet syndrome or Tuberous Sclerosis Complex.

2. Materials and methods

2.1. Study participants

CANNA-COL (CANNAbidiol COLombian registry) was a retrospective study conducted across 2 centers of reference for the treatment of epilepsy in the city of Bogota, Colombia (Hospital Occidente de Kennedy and HOMI Fundación Hospital Pediátrico la Misericordia). The study was approved by the ethics committee of both institutions (Act number 06–2021 and 51,410–21 respectively). Patients and/or their caregivers provided written informed consent for the use of anonymized data in their medical records. We included patients over two years of age with drug resistant epilepsy not related to Lennox-Gastaut syndrome, Dravet syndrome or Tuberous Sclerosis Complex, who received adjuvant treatment with a highly purified, plant-derived CBD oil-based solution (100 mg/ml) for at least three months in whom the medical record was completed with all the information required for this study.

2.2. Data collection and study variables

Information was obtained from medical records or directly from clinical interviews at each visit. The medication utilized was a highly purified, plant-derived CBD oil-based solution (100 mg/ml) with >98% CBD content and 0% THC content. It is the only highly purified CBD approved in Colombia by the National Institute of Food and Drug Surveillance (INVIMA) for use in epilepsy, with the following sanitary registration: INVIMA 2020M-0,019,590. Highly purified CBD solution was started based on the medical criteria and always as an adjuvant therapy. A treatment protocol was not included as this was a retrospective study. The treatment scheme was based on the medical criteria of the principal investigators, however, both centers adhered to the pharmaceutical recommendations of the National Institute of Drug and Food Surveillance in Colombia (INVIMA) and The Cannabinoids International Experts Panel [1]. Accordingly, all patients started with a dose of 5 mg/kg/d divided in two doses, and titration was conducted based on clinical response and tolerability. Variables included at baseline were age, sex, type of epilepsy, etiology, seizure frequency in the last month (total seizures), previous/concomitant antiseizure medication (ASM), use of non-pharmacological therapies and transaminases. Classification of seizures and epilepsies was based on International League Against Epilepsy terminology [17,18]. Variables included at the last available visit after starting CBD were current use of CBD, duration of therapy, reasons for suspension when applicable, last dose per kilogram, seizure frequency in the last month (total seizures), previous/concomitant ASM, adverse effects and transaminases. During follow-up, some patients may require a change in the ASM scheme, and this could generate a confounding bias in the efficacy of CBD. Therefore, we evaluated whether adjustments were made to the ASM scheme before and after initiating CBD. Efficacy analysis was conducted only in patients who were using CBD at the last available visit. We evaluated the percentage of patients with ≥50% reduction in seizure frequency from baseline, the mean percentage of seizure reduction from baseline and percentage of seizure-free patients (defined as no seizures since initiating CBD). Measures for seizure reduction were determined based on the frequency of seizures occurring within a month. We also included the percentage of change in the ASM scheme during the follow-up. Safety analysis was performed on all patients regardless of whether they were using CBD at the last available visit. We included adverse effects that participating physicians considered to be CBD-related. We also assessed drug-retention at the last visit and was defined as the percentage of patients who continued therapy during follow-up regardless of efficacy or adverse effects.

2.3. Statistical analysis

Statistical analysis was conducted with SPSS Statistics Version 26. Quantitative variables were expressed in terms of medians due to the distribution of the data and the presence of extreme data in the observations. The values obtained for p25 and p75 were established as IQR expressed as (IQR=p25-p75). Median differences were established using the Wilcoxon test for paired categorical variables and the Mann-Whitney test for unrelated samples. Test results with $P < 0.05$ were considered statistically significant.

3. Results

3.1. Patients

A total of 78 patients with ages between 3 and 66 years (47 adults and 31 children) were included. The median age was 24 years (IQR=9–35) and most of the patients had focal epilepsies related to a structural etiology. The included patients were highly refractory to medical treatment as they were using a median of 3 ASM (IQR=2–4) and had a median of 30 monthly seizures (IQR=12–100) before starting CBD. Additionally, 43.6% of patients had used other therapeutic alternatives such as epilepsy surgery, ketogenic diet, vagus nerve stimulation or artisanal cannabis. The baseline clinical characteristics are described in Table 1.

The median treatment time with CBD was 14 months (IQR= 10–17) and the median dose was 14 mg/kg/d (IQR= 12–18) with a range of 6.6–35 mg/kg/d. Regarding etiology, the main causes related to structural epilepsy were malformations of cortical development, sequelae of central nervous system infection and hypoxic ischemic encephalopathy. In the group of genetic epilepsies, we found a wide spectrum of pathogenic mutations without a clear predominance. The detailed description of etiologies is shown in Table 2.

3.2. Efficacy

Efficacy analysis was conducted only in patients who were using CBD at the last available visit. Sixty-one patients were included in this analysis. We found significant differences ($p< 0.01$) between the median number of seizures preCBD (median=30.0, IQR=11.5–102.5) and postCBD (median=4.0, IQR=2–15). The mean percent reduction in seizures was 67.8%. In addition, 68.8% ($n = 42$) achieved $a \geq 50\%$ reduction in seizure frequency and 11.5% ($n = 7$) achieved seizure freedom. We found no statistically significant association between the included clinical variables and the therapeutic response. We also evaluated the potential impact of concomitant clobazam (CLB) use on the efficacy of CBD and found no significant differences ($p = 0.37$) between the median number of seizures in CLB-on patients (median= 4, RIQ:1.5–13.5) and CLB-off patients (median= 5, RIQ=2.3–23–7). The mean percent seizure reduction in these patients was 53.3% and 53.4% respectively. During follow-up, the ASM scheme remained relatively stable and only in 7 cases (11%) the dose or number of ASM had to be increased due to poor efficacy. On the contrary, in 25 patients (41%) it was possible to reduce the dose or the number of concomitants ASM due to a good clinical response.

3.3. Safety

Safety analysis was performed on all patients regardless of whether they were using CBD at the last available visit. Sixty-one of 78 patients were still using CBD at the time of the last available visit showing a drug-retention rate of 78.2%. The 28.2% ($n = 22$) of patients presented adverse events related to CBD and in three cases this led to suspension of

Table 1
Baseline charateristics.

Parameter	*N* = 78
Age in years Median (IQR)	24 (9–35)
Gender: Male (Frequency, percentage)	42 (53.8)
Duration of epilepsy in years Median (IQR)	18 (7–28)
Children	6 (4–8)
Adults	26 (20–34)
Type of epilepsy (Frequency, percentage)	
Focal	68 (87.2)
Generalized	10 (12.8)
Etiology of epilepsy (Frequency, percentage)	
Structural	36 (46.2)
Unknown	27 (34.6)
Genetic	12 (17.9)
Autoimmune	1 (1.3)
Number of seizures in the last month before CBD Median (IQR)	30 (12–100)
Number of concomitant ASM before CBD Median (IQR)	3 (2–4)
Concomitant ASM (Frequency, percentage)	
Clobazam	42 (53.8)
Lamotrigine	30 (38.5)
Levetiracetam	30 (38.5)
Lacosamide	27 (34.6)
Valproic acid	25 (32.1)
Topiramate	15 (19.2)
Vigabatrin	15 (19.2)
Oxcarbazepine	12 (15.4)
Carbamazepine	11 (14.1)
Phenobarbital	10 (12.8)
Clonazepam	8 (10.3)
Divalproex	4 (5.1)
Brivaracetam	4 (5.1)
Phenytoin	1 (1.3)
Other therapeutic alternatives before CBD (Frequency, percentage)	
None	44 (56.4)
Ketogenic diet	19 (24.4)
Artisanal cannabis	9 (11.5)
Epilepsy surgery	8 (10.3)
VNS	6 (7.7)

*Patients may receive more than one medication or other therapeutic alternatives. Abbreviations: CBD: cannabidiol, ASM: antiseizure medication, VNS: vagal nerve stimulation.

Table 2
Detailed description of the etiologies included in this study.

Parameter	*N* = 78	
	Frequency (n)	Percentage (%)
Structural etiology	**36**	**46.2**
Malformation of cortical development	11	14.1
Sequelae of CNS infection	7	9.0
Hypoxic Ischemic Encephalopathy	7	9.0
Cerebrovascular disease	3	3.8
Hippocampal sclerosis	2	2.6
Posttraumatic	2	2.6
Occipital ulegyria	2	2.6
Septo-optic dysplasia	1	1.3
Neonatal Hypoglycemia	1	1.3
Unknown cause	**27**	**34.6**
Genetic etiology (gene mutations)	**14**	**17.9**
CDKL5	2	2.6
WDR62	2	2.6
ACADSB	1	1.3
CLN6	1	1.3
DARS2	1	1.3
GABRG2	1	1.3
NOTCH2	1	1.3
NOTCH3	1	1.3
NPRL3	1	1.3
STRADA	1	1.3
STXPB1	1	1.3
UBE3A	1	1.3
Autoimmune etiology*	**1**	**1.3**

* Chronic epilepsy related to Hemolytic Uremic Syndrome-associated Encephalopathy. Abbreviations: CNS: central nervous system.

Table 3
Adverse events related to CBD. Data is expressed in frequency and percentage.

Adverse events	Total *N* = 78	Range of CBD dose per kilogram			
		<10 mg/kg/d *N* = 15	11–20 mg/kg/d *N* = 40	21–30 mg/kg/d *N* = 13	>30 mg/kg/d *N* = 1
Any adverse event*	22 (28.2)	4 (26.6)	12 (30)	2 (15.4)	–
Discontinuation of treatment due to adverse events	3 (3.8)	2 (13.3)	1 (2.5)	-	-
Death**	1 (1.3)	1 (6.6)	–	–	–
Main adverse events***					
Somnolence	11	3 (20)	8 (20)	-	-
Increased seizure	(14.1)	-	3 (7.5)	1 (7.7)	-
Nausea and vomiting	4 (5.1)	1 (6.6)	3 (7.5)	-	-
Increased appetite	4 (5.1)	-	1 (2.5)	1 (7.7)	1
Dizziness/	3 (3.8)	-	2 (5.0)	-	(100)
unsteadiness	2 (2.6)	-	1 (2.5)	-	-
Impaired	1 (1.3)	-	1 (2.5)	-	-
concentration	1 (1.3)	-	-	1 (7.7)	-
Hair loss	1 (1.3)	-	1 (2.5)	-	-
Impaired sleep	1 (1.3)				-
Dysarthria					
Psychiatric adverse events	3 (3.8)	1 (6.6)	1 (2.5)	1 (7.7)	-
Irritability	2 (2.6)	-	1 (2.5)	-	-
Aggressiveness					

* The dose of CBD was unknown in 9 patients.
** A 6-year-old patient with death not related to epilepsy or CBD.
*** Patients could present more than one adverse event.

treatment. The main adverse events were somnolence (14.1%), increased seizures (5.1%), and nausea/vomiting (5.1%). Regarding psychiatric adverse events, irritability and aggressiveness was found in 6.4% of patients. The detailed description of adverse events is shown in Table 3. We evaluated the potential impact of concomitant CLB use on the safety profile of CBD and found no significant differences ($p = 0.60$) between the percentage of any adverse event in CLB-on (25%) and CLB-off patients (30.4%). Regarding somnolence, it was reported more frequently in CLB-on (19.5%) compared to CLB-off patients (6.2%), however, this difference was not statistically significant ($p = 0.09$). The analysis of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) before and after treatment with CBD was performed in 36 patients and no statistically significant differences were found. The median value of AST and ALT before and after the start of CBD was 18–18 U/L and 17–23.5 U/L respectively. None of the patients presented a clinically relevant elevation of transaminases (defined as an elevation of three times the normal value).

4. Discussion

This was a multicenter retrospective study in a real-world setting that showed that highly purified CBD is safe and effective for the treatment of drug resistant epilepsy not related to Lennox-Gastaut syndrome, Dravet syndrome or Tuberous Sclerosis Complex. The included patients were highly refractory to medical treatment as they were using a median of three ASM and had a median of 30 monthly seizures before starting CBD. Additionally, 43.6% of patients had previously used other therapeutic alternatives such as epilepsy surgery, ketogenic diet, vagus nerve stimulation or artisanal oil cannabis. In this difficult-to-treat population,

CBD reduced mean seizure frequency by approximately 68%, and nearly seven in 10 CBD-exposed patients achieved $a \geq 50\%$ reduction in seizure frequency. In this study, a special emphasis was placed on the detailed description of the etiology and a wide spectrum of mainly structural and genetic causes was shown. This is important as CBD is only approved for the treatment of some specific epileptic syndromes, however, as mentioned before, the mechanism of action of CBD in epilepsy is multifactorial and is involved in the modulation of neuronal calcium mobilization and adenosine signaling [9–11].

None of these mechanisms is directly linked to a "precision" therapeutic approach for the epileptic syndromes approved for CBD treatment. Instead, they represent a broad spectrum of action associated with the modulation of neuronal hyperexcitability, which is a characteristic of epilepsy regardless of its underlying cause [8]. In line with this, some recent studies have described that CBD could be useful across a wide range of epileptic disorders with different etiologies. For example, Laux et al. showed the results of an expanded access program and described the long-term efficacy and tolerability of CBD in several types of epilepsy not only related to Lennox-Gastaut syndrome or Dravet syndrome [12]. In this study, most of the patients had epilepsies of different etiologies that were classified in the group of "others" and corresponded to "refractory epilepsy", "idiopathic generalized epilepsy" and "intractable epilepsy" among others. In this group of patients, the efficacy analysis was similar to that observed for the Lennox-Gastaut and Dravet syndrome cohort with a therapeutic response (≥50% reduction in seizure frequency) of 49% at the end of the follow-up (week 96) [12]. Another more recent study, published by Szaflarski et al., using the same cohort of patients but with a longer follow-up time (192 weeks), showed similar results: 51% of patients achieved $a \geq 50\%$ reduction in seizure frequency [14]. This study demonstrated that the efficacy of CBD in the treatment of drug-resistant epilepsy of different etiologies is maintained over time and is useful in the long term [14]. These findings align with our results, which showed sustained efficacy during a median treatment time of 14 months. A retrospective multicenter study performed in 16 epilepsy centers in Germany found similar results and a recent systematic review showed that response to treatment with a highly purified CBD can be seen across a broad range of epilepsies with different etiologies [13,15].

Highly purified CBD treatment was generally well tolerated, and drug-retention rate at the time of the last available visit was nearly 80%. Due to the retrospective nature of this study, we did not perform an active search for adverse effects. We only included adverse effects reported by patients/caregivers that were considered to be CBD-related. The most frequently reported adverse events were somnolence, increased seizures and nausea/vomiting. This safety profile is similar to that reported in previous open-label and controlled trials [3–7,12–16, 19,20], however, a lower incidence of adverse effects was found and this could be related to the lower dose of CBD used in this study (median dose of 14 mg/kg/d; IQR=12–18). In this regard, one study found that in children with treatment resistant Dravet syndrome, adjunctive cannabidiol at doses of 10 to 20 mg/kg/d led to similar clinically relevant reductions in seizure frequency with a better safety and tolerability profile for the 10 mg/kg/d group [4].

Another important finding is that the main concomitant ASM used in this study was CLB. This could be controversial as some initial observations suggested that the efficacy of CBD was related to a pharmacokinetic interaction with CLB rather than intrinsic antiseizure activity [21]. CBD is known to increase the steady-state concentrations of CLB and N-desmethylclobazam by approximately 60% and 500% respectively [22], and this has been the reason for repeated suggestions that the antiseizure efficacy of CBD is merely explained by enhancing CLB exposure [21,23]. However, several preclinical and clinical studies have shown that antiseizure activity of CBD is independent of its interactions with CLB. For example, Anderson et al. showed that combination of CBD-CLB treatment resulted in greater antiseizure efficacy in Scn1a+/− mice, but only when an antiseizure dose of CBD was used [23]. In the same study, a novel pharmacodynamic mechanism characterized by a positive allosteric modulation of GABAA receptor activation was found [23]. A meta-analysis of randomized controlled trials showed that CBD was associated with a higher rate of seizure response in comparison to placebo when added to the existing antiseizure regimen both in patients taking and in those not taking concomitant CLB [24]. This is in line with our results that showed no significant differences ($p = 0.37$) between the median number of seizures after treatment with CBD in CLB-on and CLB-off patients with a mean percent seizure reduction of 53.3% and 53.4% respectively.

This study has limitations associated with its retrospective nature. It is a study based on health records, in addition to that, the sampling method employed was consecutive or sequential, where subjects were selected one after the other in a continuous manner. For these reasons, the data cannot be extrapolated to the entire population. The risk of missing relevant information from records and lack of randomization and blinding, which may introduce bias, is also an important limitation, however it is important to note that during follow-up, the ASM scheme remained relatively stable and only in 7 cases (11%) the dose or number of ASM had to be increased due to poor efficacy, so its assumable that the described efficacy data is directly related to CBD. Despite these limitations, this is a real-world study that better reflects the clinical setting in which CBD is used as an adjuvant therapy for the treatment of drug resistant epilepsy of different etiologies.

Conclusions

In a real-world setting, highly purified CBD has been shown to be safe and effective for the treatment of drug resistant epilepsy not related to Lennox-Gastaut syndrome, Dravet syndrome or Tuberous Sclerosis Complex. This aligns with the hypothesized mechanism of action of CBD in epilepsy which is multifactorial. Rather than being a "precision" medicine, it is associated with a broad spectrum of actions related to the modulation of neuronal hyperexcitability. Based on these findings, highly purified CBD should be considered as an adjuvant therapy for drug resistant epilepsy, regardless of its underlying cause or specific syndrome. Nevertheless, this assumption should be validated through further controlled trials.

Declaration of Competing Interest

No conflicts of interest exist.

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