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Cannabidiol as an adjuvant treatment in adults with drug-resistant focal epilepsy

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ABSTRACT

Cannabidiol oil (CBD) has been approved as an anti-seizure medication for the treatment of uncommon types of epilepsy, occurring in children: Dravet syndrome, Lennox-Gastaut syndrome, and Tuberous Sclerosis Complex. There are few publications in relation to use the CBD in adult patients with focal drug-resistant epilepsy. The objective of this study was to evaluate the efficacy, tolerability, safety, and quality of life, of adjuvant treatment with CBD, in adult patients with drug-resistant focal epilepsy for at least 6 months.

An open, observational, prospective cohort study was conducted using a before-after design (time series) in adult patients undergoing outpatient follow-up in a public hospital in Buenos Aires, Argentina.

From a total of 44 patients, 5% of patients were seizure-free, 32% of patients reduced more than 80% of their seizures and 87% of patients reduced 50% of their monthly seizures. Eleven percent presented a decrease of less than 50% in seizure frequency.

The average final dose was 335 mg/d orally administered. Thirty-four percent of patients reported mild adverse events and no patient reported severe adverse effects. At the end of the study, we found in most patients a significant improvement in the quality of life, in all the items evaluated.

Adjuvant treatment with CBD in adult patients with drug-resistant focal epilepsy was effective, safe, well tolerated, and associated with a significant improvement in their quality of life.

1. Introduction

Numerous reports over thousands of years have described the use of cannabis as a therapeutic option in various pathologies [1]. These include descriptions of the benefit of cannabis for epilepsy until the publications of observational trials, mostly appearing in the 70s [2–4]. In the1930's, the prohibition of its use in the United Nations and its classification as a controlled substance caused a sharp decrease in its utilization. Despite the prohibition in the last 2 decades, the interest of patients in cannabis treatment has resurfaced in conjunction with the discovery of cannabinoid receptors and the system called endocannabinoid. The 1990 s started a period of decriminalization and investigation progressive [5–6].

Between 2000 and 2017, 29 U.S. states legalized the use of medical cannabis and, as of 2015, eight states legalized the recreational use of cannabis in adults.

In 2012 the Uruguayan government presented an act proposing the regulation of the importation, production, acquisition, storage, marketing, and distribution of cannabis and its derivatives for social use, which was approved by the legislature the following year (2013) [7].

In 2018, Canada passed a national law, becoming the first G20 country to fully regulate the cannabis market.

In December 2020, the United Nations (UN) Commission on Narcotic Drugs (CND), re-classified cannabis and cannabis resin under an international listing that recognizes its medical value. The CND voted on recommendations made by the WHO's 41st Expert Committee on Drug Dependence (ECDD). Previously, in 2018, WHO's ECDD advised that certain cannabis-derived medicines like cannabidiol have no potential to be abused or cause dependence but have significant health benefits for children with treatment-resistant epilepsy, and therefore should not be placed under international control [8].

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The scientific contributions in relation to the cannabis plant, the discovery of the endocannabinoid system, and the evidence of its efficacy contributed to a process of acceptance by health professionals and researchers in the use of cannabis as a therapeutic option. The prohibition of its use, in this last century, did not avoid its tradition from being maintained in the communities that continued to use cannabis as an alternative to different treatments [9].

Even though there are more than 20 different types of drugs available to treat epilepsy, 30 to 40% of patients continue to have seizures. Even the appearance in the last decades of new drugs has not achieved a substantial reduction in the proportion of patients with drug-resistant epilepsy [10–11].

Highly purified cannabidiol (CBD) oil derived from cannabis sativa is to date the only cannabinoid drug that has demonstrated anticonvulsant activity in well-designed randomized placebo-controlled trials [12].

Cannabidiol was approved in 2018 by the Food and Drug Administration, United States (FDA) as an anti-seizure medication for the treatment of Dravet syndrome and Lennox-Gastaut syndrome. A year later it was approved by the European Medicines Agency (EMA) with the same indications. The FDA included Tuberous Sclerosis Complex among the diseases approved for treatment with cannabidiol in 2022 [13–15].

There are few publications concerning the use of CBD as a treatment for drug-resistant focal epilepsy in the adult population [16–17].

Clinical efficacy of adjunctive treatment with CBD has been demonstrated in five placebo-controlled pivotal trials, two of which were conducted in Dravet Syndrome (DS) [18–19], two in Lennox Gastaut Syndrome (LGS) [20–21], and one in epilepsy associated with Tuberous Sclerosis Complex (TSC) [22]. In these trials, CBD treatment resulted in a significant reduction in the frequency of convulsive seizures associated with DS, drop attacks associated with LGS, and focal and generalized seizures associated with TSC [23].

Observational studies generate inferences from the direct observation of the effect of an intervention –exposure- on subjects [24–25]. These kinds of studies have served a wide range of purposes, on a continuum ranging from the discovery of new findings to the confirmation or refutation of previous findings, benefits, and harms of medical interventions. The advantage of observational trials is that they are considerably cheaper, more practical, and feasible to conduct. Moreover, their results are more generalizable to geographically or demographically defined populations. These studies are more appropriate for establishing action-oriented public health goals [26].

Finally, in epilepsy, there are numerous publications that, based on observational trials, demonstrated the efficacy of cannabis in drug-resistant epilepsy, with a low presence of adverse effects [27–30].

The objective of this study was to evaluate the efficacy, tolerability, safety, and quality of life (QOLIE) of adjuvant treatment with CBD, in adult patients with drug-resistant focal epilepsy for 6 months.

2. Materials and methods

An open, observational, prospective cohort study was conducted using a before-after design (time series) in patients from a public hospital in Buenos Aires, Argentina, for at least 6 months.

The cohort consists of 55 adult patients between 18 and 60 years, with a diagnosis of drug-resistant focal epilepsy. The study was approved by the Ethics Committee of Hospital El Cruce (the work has been carried out in accordance with The Code of Ethics of the World Medical Association), with authorization from the National Administration of Medicines, Food and Medical Technology (ANMAT). Cannabidiol used was from Hemp Meds (RSHO-X), 5,000 mg CBD, 236 ml (21 mg/ml).

2.1. Inclusion criteria

1. Age between 18 and 60 years.
2. Drug-resistant focal epilepsy.
3. Patients without response to alternative treatments: ketogenic therapy, vagus nerve stimulator, and/or epilepsy surgery.
4. Patients that are not candidates for epilepsy surgery.
6. Basal seizure frequency greater than or equal to 3 per month (recorded 3 months prior to the first consultation).
7. Pharmacological treatment with a stable dose of anti-seizure medication.
8. Patients having clobazam as an adjuvant treatment were included with doses less than 30 mg/d.
9. Comprehensible literacy levels.
10. Signature of the informed consent accompanied by a witness with the corresponding ethics protocols.

2.2. Exclusion criteria

1. Epileptic seizures secondary to metabolic, toxic, infectious, psychogenic disorders, drug abuse, and related to acute illness.
3. Patients who are pregnant or lactating.
4. Heart, kidney, liver, pancreatic, or hematologic dysfunction.
5. Patients with chronic liver disease.
6. Hypersensitivity to any of the CBD oiĺs components.
7. Progressive or degenerative neurological disease.
8. Use of cannabidiol during the last month (commercial or artisanal) on a regular intake.
9. Status epilepticus in last year's medical history.
10. Lennox-Gastaut Syndrome or Epileptic Encephalopathy.

2.3. Study design

1. Initial visit:

(a) Electronic medical history record: documentation of demographic data, personal and family medical history, the evolution of epilepsy, type of seizure, frequency of seizures, etiology of epilepsy, results of complementary studies, current medical treatment, past anti-seizure medication, and other previous non-pharmacological treatments.

(b) Blood test: blood count, glucose, hepatogram (liver function), ionogram, total cholesterol, and kidney function.

(c) Brain Magnetic resonance images (MRI): Hospital El Cruce MRI 3 T Philips Achieva (complete epilepsy protocol: volumetric T1 isotropic gradient ECHO, Bold, T2, T2 GRE, FLAIR 2D, and 3D sequences).

(d) Pregnancy test in women of childbearing age.

(e) Self-administered questionnaire QOLIE-10.

(f) The Epworth Sleepiness Scale (ESS).

The patient was given 2 bottles with a starting dose of 250 mg/-day, administered twice a day (mean: 3,5 mg/kg/day).

2. Follow-up consultations:

(a) A control visit was carried out every 4 weeks; the seizure diary and the recording of adverse events were controlled in a form specially designed for this work. A monthly pregnancy test was performed on women of childbearing age.

The CBD dose was titrated progressively according to clinical response and tolerability.

(b) Visit (3 months): self-administered questionnaire and laboratory control.

(c) Visit (6 months- final visit-): seizure diary, blood test, and self-administered questionnaire.

2.4. Data analysis

Descriptive statistics were performed, using continuous numerical variables, the mean or median as measures of central tendency and standard deviation or interquartile interval as measures of dispersion, according to the distribution of each variable. For categorical variables, absolute and relative frequencies were used as summary measures.

The means were compared with the paired Student's test or with the Wilcoxon signed-rank test, depending on the data distribution found. For ordinal variables, the Wilcoxon signed-rank test will be used, and for dichotomous variables, the McNemar. For the parametric variables, analysis of variance (ANOVA) and for non-parametric Kruskal-Wallis have been used.

2.4.1. Effectiveness

Effectiveness was evaluated using the seizure calendar. The monthly average was estimated using the formula:

$$\left[\frac{Absolute\ number\ of\ seizures\ since\ the\ last\ visit}{Days\ since\ the\ last\ visit}\right] \times 28$$

and the change in seizure frequency was calculated as Percent Seizure Frequency Change Month X =

$$\frac{(Monthly\ Seizure\ Frequency\ X) - (Baseline\ Monthly\ Seizure\ Frequency)}{(Baseline\ Monthly\ Seizure\ Frequency)}$$

Patients were been recategorized for analysis into effectiveness subgroups based on percent change in seizure frequency into three groups:

(A) Responders: Decrease number of seizures 50% or more.

(B) Non-responders: Decrease number of seizures between 0–50%.

(C) Worsening: increase number of seizures.

The statistical significance of the differences in the number of seizures at baseline versus each control visit was analyzed using a parametric test (Student's T-Test for related samples). The sequence was plotted using a time series of the daily and monthly seizure frequency of the cohort. Data from responders versus non-responders were subjected to bivariate and multivariate analysis to determine predictors of treatment failure.

2.4.2. Doses

The CBD dose was titrated monthly according to clinical response and tolerability in each visit. Patients in the responding group maintained the dose until the evaluation of the next month, while, in the non-responders and worsening group, the dose was increased to 125 mg/day.

2.4.3. Safety and tolerance

The analysis was carried out through the recording of symptoms and signs of adverse effects (AEs) of the spreadsheet filled out by the patient and their relatives, and laboratory control at 3 and 6 months.

Interactions with ADS were analyzed, especially drowsiness, through AEs form and EES results, in the group of patients taking benzodiazepines (BZD) and phenobarbital (PB).

3. Results

3.1. Evolution

Fifty-five patients were included in the trial, and 3 patients (5,4%) abandoned throughout the study due to the presence of mild gastrointestinal adverse events. Eight patients (14,5%) left the study due to protocol violations. Forty-four (80 %) patients had finished the trial.

3.2. Demographic data

The descriptive analysis is of the 44 patients who completed the clinical trial.

The age of seizure onset was between 19–60 years (mean 35, SD 10), female 66%.

The mean baseline seizure frequency by month on the first visit was 51 (SD: 63), with a median of 33. Table 1.

ILAE Focal Seizure Classification:

Focal motor with loss awareness in 10 patients, focal motor evolved bilateral in 4 patients.

Focal autonomic with loss awareness 2 patients, autonomic with loss awareness evolved bilateral 7 patients.

Focal sensorial with loss awareness 3 patients, focal sensorial with loss awareness evolved bilateral 10 patients.

Focal experiential sensorial without loss awareness 1 patient, focal experiential sensorial with loss awareness 2 patients.

Focal cognitive con impaired awareness 3 patients, focal cognitive with impaired awareness evolved bilateral 2 patients (see Table 3).

Twenty-three (52%) have focal seizures evolved to the bilateral, mean of 3,5 (SD: 6).

Epileptogenic Zone (EZ) was mesial temporal lobe in 10 patients, temporal lateral in 6 patients, and extratemporal lobe in 28 patients (14 patients with frontal EZ and 14 patients with posterior EZ.

The mean time with epilepsy was 21 years (SD: 14).

In regards to etiology, 20 patients (46%) had focal cortical dysplasia (FCD), four patients (9%) had hippocampal sclerosis, three patients (7%) found gliosis in the brain MRI with no other lesion, one patient (2%) had a tumor (primitive neuroectodermal tumors or ganglioglioma), one patient (2%) has inflammatory etiology, one patient (2%) had a vascular malformation, one patient (2%) tuberous sclerosis complex (TSC), and 13 patients (30%) presented non-lesional epilepsy.

Patients received a mean of 3 (SD: 0.8) anti-seizure medication (ASM) as an adjuvant treatment. The most used drug was levetiracetam (29 patients, 66%), carbamazepine and clonazepam (16, 36%), valproic acid (15 patients, 34%), lamotrigine (14, 32%) and lacosamide (11, 25%). In our sample, 9 patients (21%) were under treatment with clobazam (doses less than 30 mg/day). See Fig. 1.

Six (14%) patients underwent surgical treatment, and one patient (2%) had vagal nerve stimulation (VNS). None of the patients had received a ketogenic diet.

3.3. Efficacy

Patients were recategorized for analysis into effectiveness subgroups based on percent change in seizure frequency into three groups: responder (38 patients, 86%), non-responders (5, 11%), and worsening (1, 2%). Within the responding group: two patients (5%) were seizure-free, 14 patients (32%) were reduced between 80% and 99%, and 22 patients (50%), were reduced between 50% and 79% monthly seizure frequency.

The patients who were seizure-free present an FCD, one of them has undergone epilepsy surgery with poor outcome and is under treatment with clobazam. The remaining patient has TSC and she was not considered a candidate for surgery.

Worsening group: one patient presented an increase in seizure frequency even up to a dose of 500 mg/day. This patient presents non-lesional epilepsy, with right temporal EZ defined by stereoelectroncephalograpy (SEEG), currently treated with lamotrigine and valproic acid. See Table 2.

Table 1
Demographic data.

Demographic data (n 44)	
Age	19–60 (mean 35, SD 10)
Female	29 (66%)
Male	15 (34%)
IQ	Mean: 80 (SD 15)
Epilepsy evolution (years)	Mean: 21 (SD: 14).
Baseline seizure frequency (basal/month)	Mean: 52 (SD: 63) Median: 19
Seizures evolved into bilateral	Mean: 3,5 (SD: 6)
Clobazam	11 (20%)
Epilepsy surgery	6 (14%)
VNS	1 (2%)
KD	0 (0.%)

Table 1: References: IQ: intelligence quotient. VNS: vagal nerve stimulation. KD: ketogenic diet. SD: standard deviation.

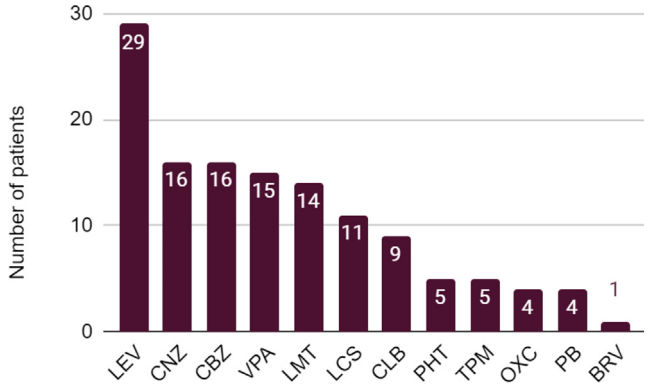

Fig. 1. Anti-seizure medication. Fig. 1: Number of patients under treatment with each anti-seizure medication. References: LEV (levetiracetam): 29 patients, 66%, clonazepam (CNZ) and carbamazepine (CBZ) 16, 36%, valproic acid (VPA) 15 patients, 34%, lamotrigine (LMT) 14, 32% and lacosamide (LCS) 11, 25%, were under treatment with clobazam (CLB) 9 patients, 21%. phenytoin (PHT), topiramate (TPM), oxcarbazepine (OXC), phenobarbital (PB), brivaracetam (BRV).

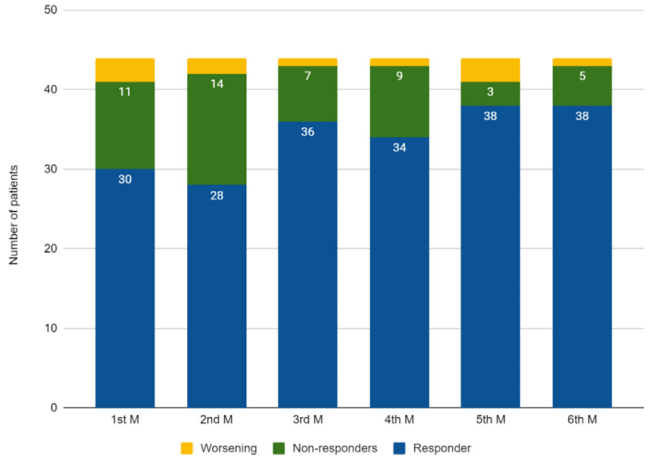

Fig. 2. Efficacy by month. Percentage of change in seizure frequency between different groups, through the time of the trial (n = 44). Fig. 2: Y-axis: number of patients by subgroups through the time of the trial. X-axis: time in months. References: Groups: Worsening (increase number of seizures), non-responders (decrease number of seizures between 0–50%), responders (decrease number of seizures by 50% or more). 1st M: first month of treatment with CBD. 2nd M: second month. 3rd M: third month, 4th M: fourth month, 5thM: fifth month, 6thM: sixth month.

No significant differences were found between the groups when the following variables were analyzed: dose at baseline and the end of the trial, number of seizures at baseline, time with epilepsy,

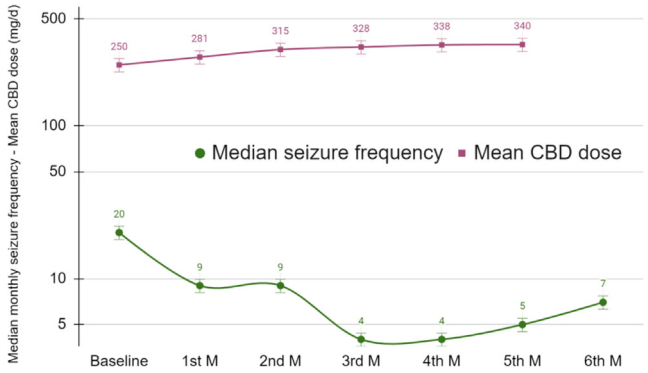

Fig. 3. Relation between median monthly seizure frequency and mean dose CBD over time (n = 44). Fig. 3: Y-axis on top: monthly mean dose. X-axis, bottom: median monthly seizure frequency. Baseline: prior to starting treatment with cannabis, 1st M: first month of treatment with CBD. 2nd M: second month. 3rd M: third month, 4th M: fourth month, 5thM: fifth month, 6thM: sixth month.

Table 2
Cannabidiol Efficacy.

Efficacy	Patients
Seizure free	2 (5%)
Reduction between 80–99%	14 (32%)
Reduction between 50–79%	22 (50%)
Reduction < 50%	5 (11%)
Increases	1 (2%)

age, use of VNS, surgery, and MRI lesion. In relation to ASM, due to the limitations of our institution, no plasma levels of clonazepam or clobazam were performed in this trial. On the other hand, the group of patients with clonazepam (16 patients) and clobazam (9 patients) did not present significant differences in efficacy, with the group that did not have any benzodiazepine.

When we analyzed the efficacy of CBD treatment and its relationship with seizure type, according to the ILAE focal seizure classification, we found no significant differences, except that at the beginning of the trial, 23 patients (52%) presented focal seizures that evolved to bilateral (mean: 3.5; SD: 6). After 6 months of treatment with CBD, 13 patients (29%) stopped having focal seizures evolved to bilateral. (Table 3).

These findings are related to the group studied; we cannot establish with certainty if, by increasing the number of subjects, these results can be modified.

3.4. CBD dose

The initial dose was 250 mg/day. The media (SD: 96) dose, at the end of the trial was 335 mg/day. The subgroup of the 38 responding patients ended with a mean of 329 mg/day.

Twenty patients (53%) completed the trial with a dose of 250 mg/d of CBD, 12 patients (32%) 375 mg/d, and 6 patients (16%) 500 mg/d.

While patients in the non-responders group had a mean dose of 350 mg/day, and the worsening group ended with 500 mg/day of CBD.

3.5. Adverse events

Fifteen patients (34%) reported no AEs. The remaining 29 patients (66%) presented mild symptoms. In this group of patients, (41%), presented one type of AEs, (11%) presented 2 AEs, and (14%), 3 types of AEs. Of patients who reported AEs, 60% were gastrointestinal (diarrhea). Three patients presented severe diarrhea that

Table 3
Efficacy by ILAE Focal Seizure Classification.

Onset	Impaired Awareness	No Impaired Awareness	Evolved Bilateral		Responders	Non Responders	Increase
			Baseline	6 months			
Autonomic (N = 9)	2	0	7	2	9	0	0
Cognitive (N = 5)	3	0	2	0	5	0	0
Sensorial (N = 13)	3	0	10	3	10	3	0
Motor (N = 14)	10	0	4	4	11	2	1
Experiential (N = 3)	2	1	0	1	3	0	0

N = patients. p-value is 0.989705.

forced the discontinuation of CBD treatment. Sixteen percent have somnolence and 14% decreased appetite.

After 1 month of treatment with CBD, we found that 6 patients reported drowsiness, 5 of them receiving clonazepam (p 0,001), 1 patient phenobarbital, and one patient receiving clobazam and clonazepam. In four patients (67%), these AEs disappears after 2 months from the beginning of the treatment with CBD.

3.5.1. Laboratory

No alterations in laboratory parameters were found during the trial.

3.6. Quality of life

The results of the QOLIE 10 questionnaire were compared at the baseline visit and the 6-month visit. We observed a significant improvement after treatment with CBD in all of the items. Thirty-one patients (70,4%) improved, 10 patients (22,7%) worsened and three patients (6,8%) had no changes. We did not observe a significant relationship between the results found for improvement in quality of life and the decrease or worsening in the frequency of seizures.

4. Discussion

We found a significant reduction in the number of monthly seizures in the majority of patients (86%) under adjuvant treatment with cannabidiol. In (29%) patients, we observed that focal seizures evolved to bilateral disappeared after treatment with CBD. We found that 5% of our population was seizure-free. Our results in terms of effectiveness and seizure free are similar to those reported by other children and adolescents research groups [31–35]. According to these reports, the occurrence of seizures free percentage is similar between adults and children.

When we compared the group of responders and the group of non-responders, we found no significant differences in the number of seizures at baseline, time of evolution, amount of anti-seizure drugs, age, and use of VNS, previous surgical treatment, ILAE Focal Seizures Classification, and MRI lesion. Similar findings in a population of adult patients with drug-resistant focal epilepsy were reported [23,36,37].

We found FCD in 46% of the included population. In different published series, the diagnosis of FCD prevalence ranges between 5% and 25%, but in specialized surgery centers such as ours, this percentage may be higher (42, 43). One hypothesis that explains this finding could be due to the exclusion of the surgical indication of the population enrolled in the trial.

Therefore, we were unable to identify variables that would help us predict response to treatment with CBD. Regarding the interaction of clobazam and clonazepam as a positive or negative variable in the efficacy with CBD, we cannot establish with certainty the interaction of clobazam and clonazepam as a positive or negative variable in the efficacy with CBD, because we should have a larger number of patients.

Regarding doses, there are few studies in adult populations, and as we previously mentioned, most of the publications are in the pediatric population, therefore doses are calculated by weight. Some authors calculated CBD doses for adult patients ranging between 200 and 300 mg/day [12]. We decided to start the treatment with a dose of 250 mg/day, according to the manufacturer's indication of the product used. The responder group of patients reduced their seizures with media doses of 329 mg/day. In the group of non-responders, seizure frequency did not improve despite the increase of doses up to 500 mg.

We did not find that CBD causes serious AEs. No author found serious AEs. In our series, three patients presented mild, poorly tolerated AEs (diarrhea), which forced us to withdraw them from the trial. According to some authors, the safety profile of CBD frequently has mild to moderate AEs [12,32,38,39]. In our study, we found no alterations in laboratory parameters.

In our experience, we observed mild and transient somnolence, significantly higher in patients who received CNZ, whereas, in the group of patients with clobazam and FB we did not observe significant changes. However, other authors [12] found that concomitant treatment with clobazam has been already shown to affect the safety profile of CBD and increase the incidence of adverse events, mainly somnolence, sedation, and pneumonia. And others present a number of indicators that were suggestive of seizure outcomes being superior in patients receiving clobazam as an adjuvant treatment [40]. A weakness of our study is that due to institutional reasons, we were unable to carry out ASM or CBD dosages.

Finally, we found in most patients a significant improvement in the quality of life in all the items evaluated. This may probably be due to a decrease in the seizure frequency, but we did not find a significant association with this variable. Some authors found that it can be explained by their excellent tolerance [41].

5. Conclusions

Adjuvant treatment with CBD in drug-resistant focal epilepsy is effective, safe, and well tolerated with low initial doses, associated with a significant improvement in quality of life.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] Li H-L. The origin and use of cannabis in eastern Asia linguistic-cultural szaimplications. Economic Botany 1974;28(3):293–301. McCoy B, Wang L, Zak M, Al-Mehmadi S, Kabir N, Alhadid K, et al. A prospective open-label trial of a CBD/THC cannabis oil in dravet syndrome. Ann Clin Transl Neurol 2018;5 (9):1077–88.

[2] Mechoulam R, Carlini EA. Toward drugs derived from cannabis. Naturwissenschaften 1978;65(4):174–9.
[3] Carlini EA, Leite JR, Tannhauser M, Berardi AC. Cannabidiol and Cannabis sativa extract protect mice and rats against convulsive agents. J Pharm Pharmacol 1973;25(8):664–5.
[4] Izquierdo I, Nasello AG. Effects of cannabidiol and of diphenylhydantoin on the hippocampus and on learning. Psychopharmacologia [Internet] 1973;31 (2):167–75. Available from: https://pubmed.ncbi.nlm.nih.gov/4578907.
[5] Matsuda LA, Lolait SJ, Brownstein MJ, Young AC, Bonner TI. Structure of a cannabinoid receptor and functional expression of the cloned cDNA. Nature 1990;346:561–4. https://doi.org/10.1038/346561a0.
[6] Devane WA, Hanus L, Breuer A, Pertwee RG, Stevenson LA, Griffin G, et al. Isolation and structure of a brain constituent that binds to the cannabinoid receptor. Science 1992;258(5090):1946–9. https://doi.org/10.1126/science.1470919.
[7] Fiore M, Pereira P. The Politics of Evaluating Cannabis Regulation in Uruguay. Novos Estudos - CEBRAP 2021;40(1):103–24.
[8] World Health Organization 2020. UN Commission on Narcotic Drugs reclassifies cannabis to recognize its therapeutic uses. https://www.who.int/news/item/04-12-2020-un-commission-on-narcotic-drugs-reclassifies-cannabis-to-recognize-its-therapeutic-uses.
[9] Kochen S, Cannabis medicinal, Editorial. Salud Colectiva, Universidad Nacional de Lanús, 2022. ISSN 1669-2381 | EISSN 1851-8265 | doi: 10.18294/sc..3991.
[10] Kwan P, Arzimanoglou A, Berg AT, Brodie MJ, Hauser WA, Mathern G, et al. Definition of drug resistant epilepsy: Consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010;51 (6):1069–77.
[11] Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs a 30-year longitudinal cohort study. JAMA Neurol 2018;75(3):279–86.
[12] Franco V, Perucca E. Pharmacological and Therapeutic Properties of Cannabidiol for Epilepsy. Drugs [Internet] 2019;79(13):1435–54. Available from: https://doi.org/10.1007/s40265-019-01171-4.
[13] EMA 2019: https://www.ema.europa.eu/en/medicines/human/EPAR/epidyolex.
[14] FDA 2018: https://www.fda.gov/news-events/press-announcements/fda-approves-first-drug-comprised-active-ingredient-derived-marijuana-treat-rare-severe-forms.
[15] FDA 2022: https://www.fda.gov/news-events/press-announcements/fda-approves-new-indication-drug-containing-active-ingredient-derived-cannabis-treat-seizures-rare.
[16] Gaston T, Szaflarski JP. Cannabis for the Treatment of Epilepsy: an Update. Curr Neurol Neurosci Rep 2018;18(11).
[17] Devinsky O, Marsh E, Friedman D, Thiele E, Laux L, Sullivan J, et al. Cannabidiol in patients with treatment-resistant epilepsy: an open-label interventional trial. Lancet Neurol 2016;15:270–8.
[18] Devinsky O, Cross JH, Laux L, Marsh E, Miller I, Nabbout R, et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome Available from. N Engl J Med 2017;376(21):2011–20. https://www.ncbi.nlm.nih.gov/pubmed/28538134.
[19] Miller I, Scheffer IE, Gunning B, Sanchez-Carpintero R, Gil-Nagel A, Perry MS, et al. GWPCARE2 Study Group. Dose-ranging effect of adjunctive oral cannabidiol vs placebo on convulsive seizure frequency in Dravet syndrome: a randomized clinical trial. JAMA Neurol 2020;77(5):613–21. https://doi.org/10.1001/jamaneurol.2020.0073.
[20] Devinsky O, Patel AD, Cross JH, Villanueva V, Wirrell EC, Privitera M, et al. GWPCARE3 Study Group. Effect of cannabidiol on drop seizures in the Lennox-Gastaut syndrome. N Engl J Med 2018;378(20):1888–97. https://doi.org/10.1056/NEJMoa1714631.
[21] Thiele EA, Marsh ED, French JA, Mazurkiewicz-Beldzinska M, Benbadis SR, Joshi C, et al. GWPCARE4 Study Group, 2018 17. Cannabidiol in patients with seizures associated with Lennox-.
[22] Thiele EA, Bebin EM, Filloux F, Kwan P, Loftus R, Sahebkar F, et al. Long-term cannabidiol treatment for seizures in patients with tuberous sclerosis complex: An open-label extension trial. Epilepsia 2021;63(2):426–39.
[23] Lattanzi S, Trinka E, Striano P, Rocchi C, Salvemini S, Silvestrini M, et al. Highly Purified Cannabidiol for Epilepsy Treatment: A Systematic Review of Epileptic Conditions Beyond Dravet Syndrome and Lennox-Gastaut Syndrome. CNS Drugs [Internet] 2021;35(3):265–81. Available from: https://doi.org/10.1007/s40263-021-00807-y.
[24] Carlson MDA, Morrison RS. Study Design, Precision, and Validity in Observational Studies Available from. J Palliative Med [Internet] 2009;12 (1):77–82. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2920077/.
[25] Bosdriesz JR, Stel VS, van Diepen M, Meuleman Y, Dekker FW, Zoccali C, et al. Evidence-based medicine—When observational studies are better than randomized controlled trials. Nephrology 2020;25(10):737–43.
[26] Metelli S, Chaimani A. Challenges in meta-analyses with observational studies. Evidence Based Mental Health 2020;23(2):83–7.
[27] Rosenberg EC, Louik J, Conway E, Devinsky O, Friedman D. Quality of life in childhood epilepsy in pediatric patients enrolled in a prospective, open-label clinical study with cannabidiol. Epilepsia 2017;58(8):96–100.
[28] Devinsky O, Verducci C, Thiele EA, Laux LC, Patel AD, Filloux F, et al. Open-label use of highly purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. Epilepsy Behav 2018;86:131–7.
[29] Szaflarski JP, Bebin EM, Comi AM, Patel AD, Joshi C, Checketts D, et al. Long-term safety and treatment effects of cannabidiol in children and adults with treatment resistant epilepsies: expanded access program results. Epilepsia 2018;59(8):1540–8.
[30] Kochen S, Manin A, Montiel R. Artisanal Cannabis in Young and Adults Patients with Treatment Resistant Epilepsy: Prospective, Observational, Open-Label Study in Argentina. J Neurol Neurol Disorders 2018;4(2):202. https://doi.org/10.15744/2454-4981.4.202.
[31] Devinsky O, Cilio MR, Cross H, Fernandez-Ruiz J, French J, Hill C, et al. Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. Epilepsia 2014;55(6):791–802.
[32] Szaflarski JP, Devinsky O, Lopez M, Park YD, Zentil PP, Patel AD, et al. Long-term efficacy and safety of cannabidiol in patients with treatment-resistant epilepsies: Four-year results from the expanded access program. Epilepsia [Internet] 2022. , https://pubmed.ncbi.nlm.nih.gov/36537757/.
[33] Hausman-Kedem M, Menascu S, Kramer U. Efficacy of CBD-enriched medical cannabis for treatment of refractory epilepsy in children and adolescents. An observational, longitudinal study. Brain Dev 2018;40:544–55.
[34] Pesántez Ríos G, Armijos Acurio L, Jimbo Sotomayor R, Cueva V, Pesántez Ríos X, Navarrete Zambrano H, et al. A Pilot Study on the Use of Low Doses of CBD to Control Seizures in Rare and Severe Forms of Drug-Resistant Epilepsy. Life 2022;12:2065. https://doi.org/10.3390/life12122065.
[35] Caraballo R, Reyes G, Demirdjian G, Huaman M, Gutierrez R. Long-term use of cannabidiol-enriched medical cannabis in a prospective cohort of children with drug-resistant developmental and epileptic encephalopathy. Seizure 2022;95:56–63.
[36] Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel C, Gagliardi R, et al. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. Pharmacology 1980;21:175–85.
[37] Nenert R, Allendorfer JB, Bebin M, Gaston TE, Grayson LE, Houston JT, et al. Cannabidiol normalizes resting-state functional connectivity in treatment-resistant epilepsy. Epilepsy Behav 2020;112:. https://doi.org/10.1016/j.yebeh.2020.107297 020107297.
[38] Billakota S, Devinsky O, Marsh E. Cannabinoid therapy in epilepsy. Curr Opin Neurol 2019;32(2):220–6.
[39] Perucca E. Cannabinoids in the Treatment of Epilepsy: Hard Evidence at Last? Available from J Epilepsy Res [Internet] 2017;7(2):61–76. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5767492/.
[40] Huestis MA, Solimini R, Pichini S, Pacifici R, Carlier J, Busardò FP. Cannabidiol Adverse Effects and Toxicity. Curr Neuropharmacol [Internet] 2019;17 (10):974–89. Available from: https://www.ncbi.nlm.nih.gov/pubmed/31161980.
[41] Von Wrede R, Helmstaedter C, Surges R. Cannabidiol in the Treatment of Epilepsy. Clin Drug Invest 2021;41(3):211–20.