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Research Paper

Psychiatric comorbidities before and after cannabidiol treatment in adult patients with drug resistant focal epilepsy

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ABSTRACT

Cannabidiol oil (CBD) has been approved as an antiseizure medication for the treatment of drug −resistant epilepsy in pediatric patients in 2018 for some special types of epilepsy. Since this time its use was extended to other forms of epilepsy. However, to date, there are few publications on the use of CBD in adult patients with drug-resistant focal epilepsy and psychiatric comorbidities.

We conducted a prospective, observational, open cohort study, with a before-after design, in adult patients, we assessed the effectiveness, dosage, and tolerance of adjunctive CBD treatment. Our study concluded that CBD was effective and safe.Our study in line with others examining CBD use in adult patients with drug-resistant epilepsy, omits consideration of psychiatric aspects.

The aim of this study was to evaluate, in the same patient population that was part of a previous observational study, depression, quality of life, anxious symptoms and daytime sleepiness before and after CBD treatment.

Results: Forty-four patients were enrolled in the study. Prior to CBD treatment, 50 % of participants exhibited symptoms of depression. Following CBD treatment, 95.4 % of these individuals demonstrated a marked improvement ($p = 0.001$). Among this cohort, 71.5 % of patients reported minimal or no depressive symptoms post-treatment. Moreover, 68 % of patients experienced an enhancement in their overall quality of life.

Comparative analysis of BDI-II and QOLIE-10 scores before and after CBD treatment revealed a statistically significant positive correlation ($p < 0.036$ and < 0.001, respectively). Improvements in depressive symptoms were found to correspond with enhancements in quality of life. In terms of anxiety symptoms, 54.5 % of patients exhibited such symptoms prior to CBD treatment, with 71 % showing improvement post-treatment.

Adjunctive CBD treatment in adult patients with drug-resistant focal epilepsy was effective, safe, well tolerated and associated with significant improvement in depressive symptoms, anxiety and quality of life.

1. Introduction

Over the years, numerous publications have detailed the utilization of cannabis as a therapeutic option across various pathologies. In recent times, healthcare practitioners and researchers have increasingly embraced cannabis as a therapeutic option, prompted by scientific findings underscoring its clinical efficacy [1,2,3,4,5].

Despite the availability of over 20 different drug types for epilepsy treatment, a substantial proportion of patients, ranging from 30 to 40 %, continue to experience seizures. The emergence of new drugs in recent decades has not significantly decreased the prevalence of drug-resistant epilepsy among patients [6,7].

Highly purified cannabidiol (CBD) oil derived from cannabis sativa stands as the sole cannabinoid drug to date exhibiting anticonvulsant activity in well-designed randomized placebo-controlled trials [8,9,10]. Cannabidiol oil was approved in 2018 by the U.S. Food and Drug Administration (FDA) as an anticonvulsant drug for the treatment initially of severe encephalopathies likeDravet syndrome and Lennox-Gastaut syndrome, which are most frequent in the pediatric population. A year later it was approved by the European Medicine Agency (EMA) with the same indications. The FDA included Tuberous Sclerosis Complex among the diseases approved for CBD treatment in 2022.

Despite scant literature on CBD's efficacy in treating drug-resistant focal epilepsy in the adult population, our recent publication showed the efficacy and safety of CBD as adjunctive use in adults with drug-resistant focal epilepsy. Our study in line with others examining CBD

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use in adult patients with drug-resistant epilepsy, omits consideration of psychiatric aspects[11].

The present research, specifically explore the CBD impact on the psychiatric aspects in the same population of patients studied [10,11].

Psychiatric comorbidities afflict approximately 30–50 % of patients with drug-resistant epilepsy, with prevalent disorders including depression, anxiety, psychosis, impulsivity, personality disorders, somatoform, and functional disorders[12,13,14]. The presence of psychiatric comorbidities may affect the prognosis of epilepsy, especially in patients who have undergone surgery. Preoperative psychiatric symptoms correlate with high seizure frequency, which is a complex interaction as evidenced by prior publications[15,16].

Our study further incorporates an evaluation of quality of life (QOL) to delineate each patient's mood self-perception [17].

The endocannabinoid system (ECS)[18,19] currently emerges as a promising therapeutic target for developing anxiolytic drugs, attributed to its role in neuromodulating synaptic plasticity and neuronal activity pertinent to anxiety and depression responses.

The aim of this study was to assess psychiatric and related symptoms, particularly depression, anxiety, quality of life, and symptoms and daytime sleepiness before and after CBD treatment in a cohort of adult patients with drug-resistant focal epilepsy.

2. Materials and methods

A prospective, observational, open cohort study was carried out using a before-after design (time series) in patients of a specialized epilepsy center in a public hospital [10]. This is an observational trial conducted over 6 months, following a protocol designed specifically for this study, which allows us to reach consistent conclusions. Since our trial was observational, it did not include a control group, as typically employed in double-blind placebo-controlled studies [20,21].

The cohort comprised 55 adult patients aged between 18 and 60 years, diagnosed with drug-resistant focal epilepsy.

We classified the type of seizures according to ILAE Focal Seizure Classification [7].

The antiseizure medication (ASM) treatment received at the time the patient enrolled in the trial remained stable until the end. The study received approval from the Ethics Committee of El Cruce Hospital. The cannabidiol used was donated by Hemp Meds (RSHO-X), (5000 mg CBD bottle, 236 ml (21 mg/ml)).

2.1. Inclusion criteria

- Age between 18 and 60 years old.
- Drug-resistant focal epilepsy, defined by ILAE, as a failure of adequate trials of two tolerated, appropriately chosen and used antiseizures medications (ASMs) schedules (whether as monotherapies or in combination) to achieve sustained seizure freedom [6].
- Patients with no response to alternative treatments: ketogenic therapy, vagus nerve stimulator and/or epilepsy surgery.
- Patients who are not candidates for epilepsy surgery.
- Frequency of baseline seizures greater than or equal to 3 per month in the last 3 months before the first consultation, as documented in seizure diaries completed by the patients.
- Pharmacological treatment with stable anticonvulsant medication doses throughout the trial.
- Patients receiving clobazam as adjuvant treatment with doses lower than 30 mg/d were included.7. IQ 〉 70, that they were able to understand the instructions and complete the scales.
- All patients signed an informed consent accompanied by a witness with the corresponding ethics protocols.

2.2. Exclusion criteria

- Epileptic seizures secondary to metabolic, toxic, infectious, psychogenic and drug abuse.
- Patients who are pregnant or breastfeeding.
- Cardiac, renal, hepatic, pancreatic or hematologic dysfunction.
- Patients with chronic liver disease.
- Hypersensitivity to any of the components of CBD.
- Progressive or degenerative neurological disease.
- Use of cannabidiol during the last month (commercial or artisanal) in regular intake.
- Presence of status epilepticus in the last year. Lennox Gastaut Syndrome; Syndrome Dravet; encephalopathy epileptic.
- Psychosis.

2.3. Study design

2.3.1. Initial visit

- Electronic medical record: documentation of demographic data, personal and family medical history, evolution of epilepsy, type of seizures, frequency of seizures, etiology of epilepsy, results of complementary studies, current medical treatment, past ASM, and other previous non-pharmacological treatments.
- Blood tests: hemogram, glucose, hepatogram (liver function), ionogram, total cholesterol and renal function.
- Pregnancy test in women of childbearing age.
- Detailed semi-structured psychiatric interview for the main diagnoses of Axis I of the DSM V [22] also carrying out a complete semiological examination, evaluating higher functions such as attention, memory, thinking, lucidity and volitional attitude [23]
- Self-administered questionnaire Mental Health (BDI-II, HADs, QOLIE 10, ESS) once the clinical interview is completed.
- The patient was given 2 bottles with a starting dose of 250 mg/day, administered twice a day. We use the recommended initial dose for adult patients [12,24].

2.3.2. Follow-up consultations

- During each control visit, which occurred every 4 weeks, patients filled out a seizure diary in a paper format specifically tailored for this trial. Additionally, at each visit, physicians conducted a thorough assessment using a detailed questionnaire, administered to both the patient and their family, to ascertain the frequency of seizures and the presence or absence of adverse effects.
- Furthermore, women of childbearing age underwent a monthly pregnancy test.
- Visit (3 months): self-administered questionnaire (BDI-II, HADs, QOLIE 10, ESS) and laboratory control.
- Visit (6 months −final visit-): blood tests and mental health questionnaires (BDI-II, HADs, QOLIE 10, ESS)
- Patients remained on the initial dosage of 250 mg/day, administered twice daily. The CBD dose was gradually adjusted based on clinical response and tolerability. Dose escalation was, in the event of inadequate response, 1 ml (=100 mg) each control visit, up to 500 mg per day. The ASM doses were not modified while the patients were enrolled in the clinical study.

2.4. Protocol of scales and questionnaires used in the evaluation of mental Health

A) Beck Depression Inventory (Beck Depression Inventory − BDI-II):

The Beck Depression Inventory [25,26,27] is a self-administered questionnaire, composed of 21 items in multiple-choice format. This tool has 2 domains, the first called Affective Cognitive Factors,

composed of 16 subdomains, and the Somatic Factor with 5 subunits. A total of 21 subdomains scored from 0 (min) to 63 (max) as follows: Minimal or no depression: 0 to 13, Mild depression: 14 to 19, Moderate depression: 20 to 28, and Severe depression: 29–63.

Patients were grouped according to the level of severity of their depressive symptoms. This scale covers all DSM-IV diagnostic criteria for major depressive disorder and is a reliable indicator of symptom severity and suicidal thoughts. Its validity and case-finding ability as a screening tool are well established.

B) Hospital Anxiety and Depression Scale (HAD):

The HADs scale [30] is an instrument designed to detect non-somatic affective disorders, both in hospital and community settings. These symptoms include: insomnia, fatigue, weight loss and/or weight gain and/or appetite.

It is a 14-item self-administered instrument consisting of a depression subscale (HAD- D) and an anxiety subscale (HAD-A) with interspersed items. These are scored on a 4-point Likert frequency scale (0–3) with a total score ranging from 0 to 21 on each item.

A score between 8 and 10 is considered a clinically significant disorder, and greater than/equal to 11, moderate- severe.

C) Quality of Life (QOLIE 10):

The Quality of Life in Epilepsy Inventory (QOLIE) 10 [28,29] was developed by Cramer et al in 1996 as a reduced version of the QOLIE-31, with very similar results. The Spanish version was developed in 2008. The QOLIE-10 consists of 10 questions and is divided into two factors that assess the patient's condition in the last four weeks:

a) implications of epilepsy (physical and psychological effects of antiepileptic treatment, preoccupation with seizures, difficulty in transportation, work and social limitations).
b) mental health (memory, vital energy, depression and general quality of life). Each answer awards between 1 and 5 points.

Each of the questions is evaluated from 1 to 5, with a better quality of life if the final score is 10 and a worse quality of life if it is 50: Good quality of life (10 to 20), Fair (21 to 35) and Poor quality of life (36 to 50 points).

D) Epworth Daytime Sleepiness Scale (ESS):

The Epworth Sleepiness Scale [31] (ESS) is a self-administered questionnaire based on 8 questions. Respondents are asked to rate, on a 4-point scale (0, 1, 2, 3)*, their usual likelihood of falling asleep while doing eight different activities. Most people do these activities at least occasionally, although not necessarily every day.

According to the score given to each question, the degree of daytime sleepiness could be classified as: No daytime sleepiness (0—–5), Light daytime sleepiness (6—–10), Mild daytime sleepiness (11—12), Moderate daytime sleepiness (13—15), Excessive daytime sleepiness (16—24).

2.5. Seizures control

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

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

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 re-categorized for analysis into effectiveness subgroups, according to seizure frequency, into three groups:

A) Responders: Decrease in the number of seizures by 50 % or more.
B) Non-responders: Decrease in the number of seizures between 0–49 %.
C) Worsening: increase in the number of seizures despite the increase in CBD dosage.

2.6. Data analysis

Descriptive statistics were performed. For continuous numerical variables, we used the mean or median as measures of central tendency. For measures of dispersion, we used the standard deviation or the interquartile range. For categorical variables we used absolute and relative frequencies.

Means were compared with Student's *t*-test or the Wilcoxon signed-rank test, depending on the distribution of the data. A p value of less than 0.05 was considered significant. The Wilcoxon signed-rank test was used for ordinal variables and McNemar's test for dichotomous variables. We used analysis of variance (ANOVA) for parametric variables to investigate the associations between seizures and psychiatric symptoms, and Kruskal-Wallis test for nonparametric variables.

To corroborate that the decrease in the BDI-II score was truly significant, each of the 22 patients in the "depressed" group were analyzed with the reliable change index (RCI)[32,33]. The formula is:

$$RCI = [(PEFpost - PEFpreb)/Sdif].$$

Considered statistically significant if RCI≥1.96 or RCI≤–1.96.

3. Results

3.1. Evolution

Fifty-five patients were initially included in the trial. Three (5.4 %) patients left the study due to mild gastrointestinal adverse events, while eight (14.5 %) patients discontinued participation due to protocol violations. Ultimately, 44 (80 %) patients successfully completed the trial. (Table 1).

Regarding type of seizure we found: Focal motor with loss awareness, 10 patients. Focal motor evolved bilateral, 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. (Table 2).

Regarding the localization of epilepsy, 10 patients were localized in

Table 1
Demographic data.

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

Table 2
ILAE Focal Seizure Classification.

Type of Focal Seizures	Patients (n)
Motor with loss awareness	10
Motor evolved bilateral	4
Autonomic with loss awareness	2
Autonomic with loss awareness evolved bilateral	7
Sensorial with loss awareness	3
Sensorial with loss awareness evolved bilateral	10
Experiential sensorial without loss awareness	1
Experiential sensorial with loss awareness,	2

mesial temporal lobe, 6 patients in lateral temporal lobe, and 28 patients in extratemporal lobes (14 in the frontal lobe and 14 in the parietal and occipital lobes).

In relation to ASMs in the first visit, the patients were receiving a mean of three (SD: 0.8) ASM as adjuvant treatment. The most commonly used was levetiracetam 29 (66 %) patients, followed by carbamazepine and clonazepam in 16 (36 %) patients, valproic acid in 15 (34 %) patients, lamotrigine in 14 (32 %) patients and lacosamide in 11 (25 %) patients.

With respect to non-pharmacological treatment options, six (14 %) patients underwent surgical treatment, one (2 %) patient received vagus nerve stimulation (VNS), and none of the patients had received a ketogenic diet.

Patients were reclassified for analysis into effectiveness subgroups based on the percent change in seizure frequency, resulting in three groups: responders 38 (86 %) patients, non-responders five (11 %) patients and one (2 %) patient presented worsening, with an increase in seizure frequency in 10 %, even with a dose of 500 mg/day. This patient has non-lesional epilepsy with bilateral temporal EZ identified through stereoelectroencephalography (SEEG), currently managed with lamotrigine and valproic acid, and was considered ineligible for surgery. The increase in seizures was described in a few patients, by other authors, after the use of CBD [34]. We did not find any other cause to explain the increase in the frequency of seizures than the onset of treatment with CBD (Table 3).

No significant differences were observed between groups in terms of CBD efficacy regarding the following factors: baseline seizure frequency, duration of epilepsy, number of ASMs, clobazam usage, age, VNS, surgical intervention, and MRI findings.

Concerning adverse events (AE), 15 (34 %) patients reported no AE. Among the remaining 29 (66 %) patients who experienced AE, symptoms were generally mild. Within this subgroup, 41 % of patients reported a single type of AE, 11 % reported two AE, and 14 % reported three types of AE. Among these patients, 60 % experienced gastrointestinal symptoms, primarily diarrhea. Additionally, 16 % of patients reported experiencing somnolence, while 14 % reported decreased appetite. After one month of CBD treatment, we observed that six patients reported drowsiness. Among them, five were concurrently receiving clonazepam ($p < 0.001$), one was taking phenobarbital, and one was receiving a combination of clobazam and clonazepam. However, in four (67 %) patients of this group, AE resolved within 2 months of initiating CBD treatment.

Table 3
Cannabidiol Efficacy (N=44).

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 %)

3.2. Psychiatric comorbidities

3.2.1. Beck depression Inventory – BDI-II

Before CBD treatment, from a total of 44 patients, 22 (50 %) presented criteria for depression by BDI-II, score media = 16 ("Mild Depression"), none of this patients received specific treatment in the first visit. For the analysis, we divided the total population into two subgroups, the group of patients with depressive symptoms (n = 22) and the group of patients without depressive symptoms (n = 22).

After 6 months of CBD treatment, the group of patients with depression, 21(95.4 %) presented a significant improvement ($p = 0.001$) where 15 of these 21 (71.5 %) patients presented "minimal or no depression". (Fig. 1).

Only one (4.5 %) patient remained unchanged. The RCI in each patient before and after CBD treatment confirmed the results. (Table 4).

In the group of patients without depression, one patient presented an increase in depression score (score = 22).

When we compared the results of the BDI-II with seizure frequency, after CBD treatment, we found the following results: In the responder group (n = 38), 18 (47.3 %) patients improved their depressive symptoms, 19 (50 %) patients remained unchanged and one (2.6 %) patient presented "de novo" depression. In the non-responder group (n = 5), two (40 %) patients improved their depressive symptoms and three (60 %) patients remained unchanged. The patient whose seizure frequency increased (n = 1) improved his depressive symptoms (Table 5).

3.2.2. QOLIE 10

Before CBD treatment, the median QOLIE in the total population was 24.5 points (normal QOL). After CBD treatment the median was 20 points (good QOL), where 30 (68 %) patients improved their QOL, four (9 %)patients had no change and 10 (22.7 %) patients worsened Fig. 2.

When we compared the results of the QOLIE 10 scale with the seizure frequency groups, after CBD treatment, we found the following results: In the responder group (n = 38), 28 (74 %) patients improved their QOL, three (8 %) patients remained unchanged and seven (18 %) patients worsened their QOL. In the non-responder group (n = 5), two (40 %) patients improved their QOL and three (60 %) patients worsened. The patient who increased his seizures frequency after treatment with CBD, did not present changes in the QOLIE scale (Table 6).

When we compared the BDI-II and QOLIE 10 scores at visit 1 and visit 7 (final trial), we found a significant direct relationship ($p < 0.036$ and < 0.001 respectively), when depressive symptoms improve, quality of life improves.

3.2.3. HADs

When we analyzed this instrument, we considered only anxious symptoms. Before CBD treatment 24 (54.5 %) patients had anxiety symptoms (M=11,6 "Moderate-Severe") and 20 (45.5 %) patients were normal. We divided the total population into two subgroups according to the results of the initial visit. The group of patients with anxiety symptoms (n = 24) and the group of patients without anxiety symptoms (n = 20).

After 6 months of CBD treatment, in the group of patients with anxiety symptoms, 17 (71 %) patients improved them (M=7,6 "No anxiety symptoms"), and 11 (65 %)of these patients, ended up the trial without anxious comorbidity. Four (16.6 %) patients had no change and three (12.5 %) patients had increased anxietysymptoms.

The group of patients without anxiety symptoms showed no changes, after 6 months of CBD treatment.

When we compared HAD results with seizure frequency groups after CBD treatment, we found the following results: In the responding group (n = 38), 14 (37 %) patients improved their anxious symptoms, 21 (55.2 %) patients remained unchanged and three (8 %) patients worsened their anxious symptoms.

In the non-responder's group (n = 5), three (60 %) patients improved their anxious symptoms and two (40 %) patients remained unchanged.

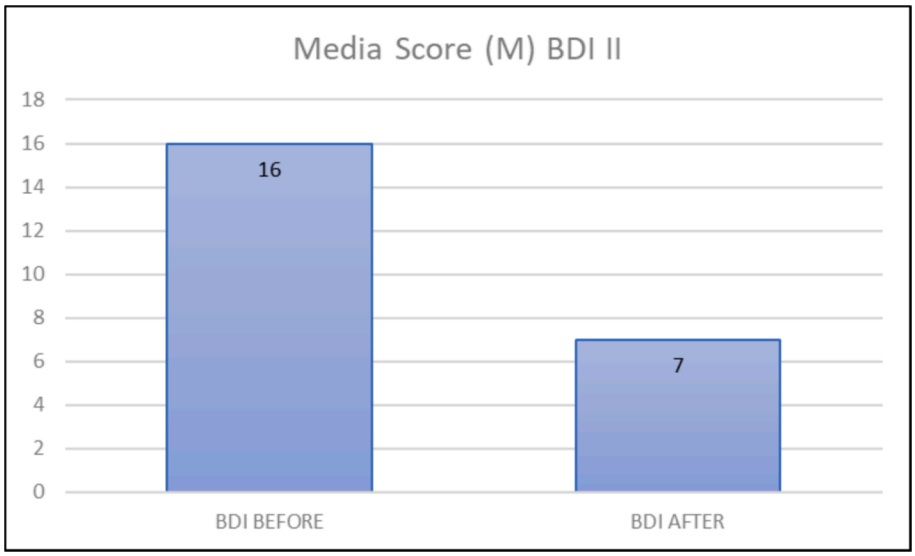


Fig. 1. BDI II Before: baseline (M=16 and SD=11.5) BDI II After: visit 7 (M=7 and SD=7). P<0.001.

Table 4
BDI II. Reliable change index (RCI) of each patient before and after CBD treatment.

PATIENS	BDI AF	BDI BF	RCI
1	12	23	−7.10
2	1	28	−17.60
3	9	28	−12.40
4	1	18	−11.11
5	0	25	−16.34
6	4	19	−9.80
7	8	24	−10.46
8	19	19	0.00
9	9	22	−8.50
10	4	18	−9.15
11	16	28	−7.84
12	21	45	−15.69
13	0	17	−11.11
14	8	43	−22.88
15	21	29	−5.23
16	11	38	−17.65
17	21	34	−8.50
18	1	19	−11.76
19	13	14	−0.65
20	21	26	−3.27
21	4	21	−11.11
22	15	27	−7.84

References: RCI≥1.96 or RCI≤−1.96 is considered significant.

The patient who worsened (n = 1), no change in baseline HADs was observed.

3.2.4. Sleep scale

Before CBD treatment 25 patients had no daytime sleepiness, 11 patients had slight daytime sleepiness, two patients had mild daytime sleepiness, three patients had moderate daytime sleepiness, and three patients had excessive daytime sleepiness, with an average of 6 points.

After 6 months of CBD treatment, we did not find significant differences. (Graph 1).

4. Discussion

The aim of this study was to evaluate depression, quality of life, anxiety, and daytime sleepiness before and after CBD treatment in adult patients with drug-resistant focal epilepsy. The population analyzed was part of a previous observational study conducted by our group, where we evaluated the effectiveness, dosage, and tolerance of adjuvant treatment with CBD (10). Our study concluded that CBD was effective and safe. We continue to investigate another population of adults with drug-resistant epilepsy, addressing additional aspects such as drug interactions, optimal doses, and CBD dosing.

There is controversy between different research studies regarding depression in the population with drug-resistant epilepsy [12,13,35,36,37]. Some of these authors, including previous publications by our group, attribute depression as a common comorbidity in this group of patients as a consequence of a chronic disease [10,15]. Other authors propose a bidirectional relationship between depression and epilepsy. This theory suggests that structural, neuropathological and neurotransmitter alterations associated with primary depression may facilitate the development of a seizure disorder spontaneously or in the presence of a central nervous system lesion [35,36,37,38,39].

However, there is consensus that in some patients, depression may be due to adverse effects of certain medications, especially levetiracetam and topiramate.

Our research was organized with a first approach with a semi-

Table 5
Relationship between BDI-II (depressive symptoms) and efficacy groups (responders, non-responders and worsened), before and after CBD treatment.

Seizure control = N	BDI-II before				BDI-II after			
	Minimal	Mild	Moderate	Severe	Minimal	Mild	Moderate	Severe
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Responders = 38	19 (50 %)	6 (15 %)	9 (24 %)	4 (11 %)	32 (84 %)*	2 (5 %)*	4 (11 %)*	–*
Non-responders = 5	3 (60 %)	1 (20 %)	1 (20 %)	–	4 (80 %)	1 (20 %)	–	–
Worsening = 1	–	–	–	1	–	–	1	–

References: N=number of patients. M=mean of the values. * P=0.05.

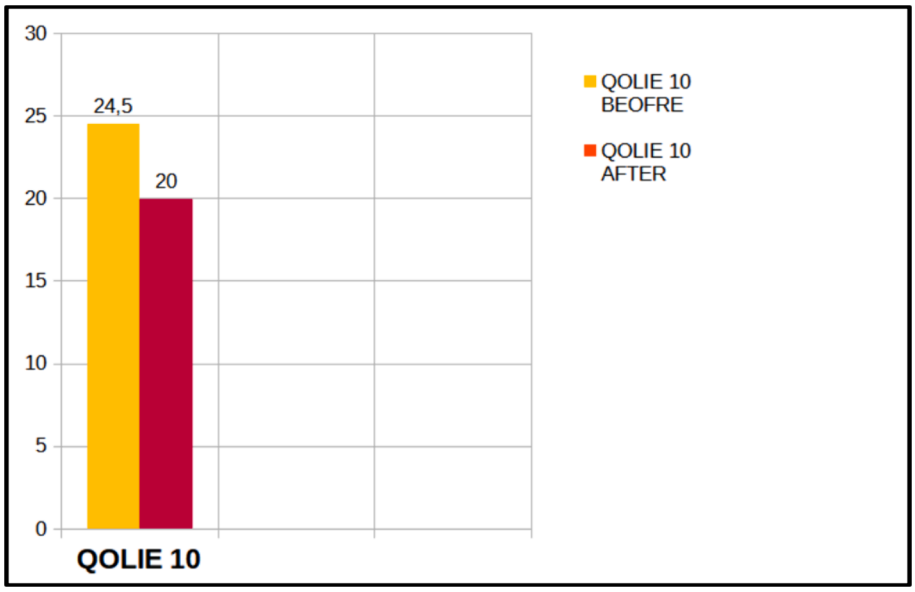
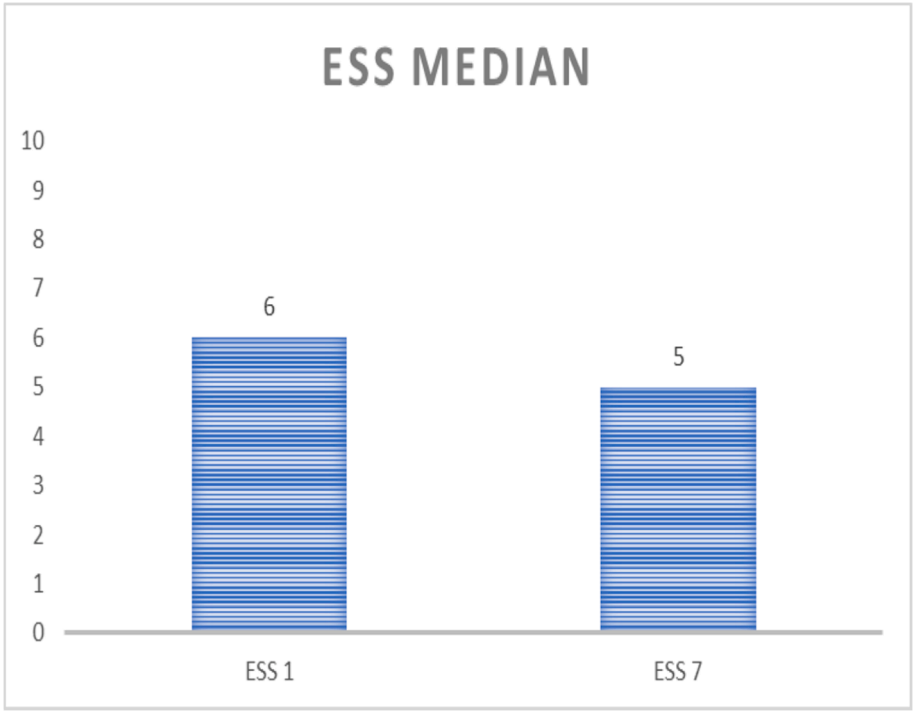


Fig. 2. Graph relating the improvement in QOLIE 10 median scores, before and after CBD treatment, in the total population. References: Qolie 10 before: (m = 24.45) Qolie 10 after (m = 20). P<0.001.

Table 6
Comparison between QOLIE 10 scores and efficacy groups, before and after CBD treatment.

Seizure control = n	Qolie 10 before				Qolie 10 after			
	Median	Good	Regular	Poor	Median	Good	Regular	Poor
		N (%)	N (%)	N (%) /M		N (%) /M	N (%) /M	N (%) /M
Responders = 38	24,5	13 (34 %)	23 (60 %)	2 (6 %) / 38	19	25 (66 %)	11 (29 %)	2(5 %) *
Non − responders = 5	23	1 (20 %)	4 (80 %)	–	24,5	1 (20 %)	4 (80 %)	–
Worsening = 1	26	–	26	–	26	–	26	–

References: N patients, M: mean. *P=0.05.



Graph 1. Epworth sleep scale before and after CBD treatment. References: Epworth sleep scale (ESS). Bar graph relating the mean scores obtained by ESS, at the beginning and at the end of the treatment with CBD, in the total population. ESS Before Visit 1: (M=6 and SD=5) ESS After Visit 7: (M=5 and SD=4). P<0,046.

structured clinical interview, with the aim of enabling the application of diagnostic tools and self-administered questionnaires. In our study, we found a remarkable finding that has been little reported in the literature, a significant improvement in depressive symptoms after treatment with CBD, findings obtained from data collected pre and post treatment, through the analysis of the BDI II, and confirmed with the RCI reliability index even in patients treated with levetiracetam. However, we were unable to provide definitive conclusions on the interaction of CBD with other ASMs due to the absence of dosage measurements of these medications. This improvement in depressive symptoms after CBD treatment may correspond to the overall improvement observed in seizure frequency. In addition, we observed improvements in depressive symptoms among non-responders. This finding may be attributed to the antidepressant and anxiolytic effects of cannabidiol, which are directly related to the endocannabinoid system, as previously described by other researchers [18,19,38,39,40]. Regarding the only patient with "de novo" depression who was in the responder subgroup, we found no cause to explain this phenomenon.

In addition, we observed improvements in quality of life, using data obtained from the QOLIE 10 scale and its subsequent analysis, among responders and those whose depressive symptoms improved, as previously described by other authors. Regarding anxiety symptoms, after treatment with CBD, we observed an improvement in the majority of the population, based on the analysis of the data obtained from the HADS scale. The improvement was independent of the CBD response in the frequency of the seizures, with a small percentage experiencing a worsening of the symptoms without an identified cause, despite belonging to the group of responders. Several publications have shown that the main signaling and communication activity within the Endocannabinoid System (ECS) is attributed to the action on the known cannabinoid receptors CB1 and CB2. The acute antidepressant effect of CBD seems to depend on the facilitation of ECS-mediated neurotransmission at 5HT1A receptors, both directly and through interaction with CB1 receptors. In animal models, this mechanism may also explain the acute antidepressant effects induced by CBD (40). As for the results of the Epworth Sleepiness Scale, the patients did not show significant changes after treatment with CBD, we do not have a clear explanation as to why no positive or negative impact was found in our population. However, it is relevant to mention that no patient reported increased sleepiness with the use of CBD unlike most other ASM.

The limitations of our study are based on the observational design without a control group. However, we have strictly followed the protocol throughout the study. Double-blind placebo-controlled trials remain the gold standard in clinical research.

5. Conclusions

In this observational study, with patients being their own controls, we observed improvements in depressive symptoms, quality of life (QOL), and anxiety; no changes were observed in daytime sleepiness associated with CBD treatment.

This improvement is likely due to the positive clinical response in seizure control, as well as the beneficial effects of CBD in modulating the endocannabinoid system. CBD proved to be an effective treatment for drug-resistant focal epilepsy in adult patients, demonstrating good tolerability and leading to improvements in the comorbid psychiatric disorders present in this study population.

Ethical considerations:

The study received approval from the Ethics Committee of Hospital El Cruce and was conducted in accordance with the Code of Ethics of the World Medical Association. All participants in the study provided informed consent by signing the appropriate documentation.

CRediT authorship contribution statement

Julián Lamonarca: Writing – original draft, Investigation, Formal analysis, Data curation. **Inés Mintz:** Methodology, Investigation, Data curation. **Liliana Bayarres:** Project administration. **Silvia Kochen:** Writing – original draft, Supervision, Investigation. **Silvia Oddo:** Writing – original draft, Supervision, Investigation.

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.

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