

Long-Term Impact in the Quality of Life of Patients with Drug-Resistant Epilepsy That Use Cannabidiol

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Abstract

Introduction: Epilepsy is considered a chronic neurological condition that manifests itself with seizures, where 30% - 40% of patients do not achieve control of their seizures despite proper management. Seizures represent a significant limitation in the patient's daily activities and are often accompanied by emotional and relational difficulties that have a great impact on the quality of life of the patient and their families. Cannabidiol (CBD) has been found to be effective in controlling seizures and may also improve cognitive and behavioral abilities. **Material and Methods:** The Quality of Life of the Patient with Epilepsy (CAVE) scale was applied to patients with refractory epilepsies who use Cannabidiol (CBD) added to their base therapy, before the use of CBD and after 12 months of follow-up. The presentation of collateral effects was also evaluated. **Results:** Out of 34 patients, 26 (76.5%) increased their CAVE value at the end of the study and only 1 (2.9%) decreased. 19 (55.9%) improved in learning and behavior, 55.8% in the frequency of seizures and 79.4% reported a decrease in the intensity of seizures. There were other positive side effects such as improvement in alertness, language, sleep and behavior. The main side effects were mild and transitory, including drowsiness, and constipation. There was a correlation between the global perception of improvement and seizure control. **Conclusions:** This study shows that in the long term CBD improves the quality of life of patients with refractory epilepsies, through the control of seizures and the improvement of cognitive and behavioral functions.

Keywords

Quality of Life, Refractory Epilepsy, Cannabidiol

1. Introduction

The World Health Organization defines Quality of Life (QoL) as the perception that an individual has of his place in existence, in the context of the culture and of the value system in which he lives and in relation to his objectives, his expectations, his norms, his concerns. Epilepsy is a chronic disease that has a great impact on the QoL of patients and their families. According to some authors, up to 58.3% of patients with epilepsy have a poor QoL due to the unexpectedness of new seizures, the probable associated injuries, the use of anticonvulsant drugs and their adverse effects [1] [2]. In addition, psychosocial problems, especially the great social stigma that still prevails around this pathology, are usually the main problem that affects the patient and the family with epilepsy [3].

Patients with Drug-Resistant epilepsy face even more complex clinical conditions, aggravated by factors such as the early onset of epilepsy, frequent and severe attacks and the use of polytherapy, all of which may cause a worse quality of life [2]. Besides, other factors that negatively affect the individual's QoL cannot be undermined, such as excessive fatigue, social isolation, low self-esteem, anxiety, depression, various degrees of cognitive dysfunction (mainly memory and concentration), lack of independence and great emotional and behavioral instability [2] [4].

In clinical practice, improving the QoL of patients with epilepsy is a daily challenge. There are many drugs used that, despite their benefits in seizures control, add more adverse effects to the scenario. For this reason, recent studies showing the effectiveness of Cannabidiol (CBD) in the control of seizures, especially in Dravet and Lennox Gastaut Syndromes [5] [6], are interesting, since, besides the seizure control, other positive side effects have also been reported. The most relevant positive effects are improvement in the level of alertness, memory, language, motor skills, sleep, mood, behavior and socialization [4] [7].

In the following section, we will assess the changes in the QoL of patients with Drug-Resistant epilepsy who have used CBD concomitantly with their base treatment for at least 12 months.

2. Methods

2.1. Study Design

This retrospective observational descriptive study evaluates QoL of patients with Drug-Resistant epilepsy that have been treated with antiepileptic medication associated with CBD for at least 12 months, through the use of diverse questionnaires that focus on seizures control and adverse effects caused by the use of multiple drugs.

2.2. Population

The study includes all the patients treated with antiepileptic medication associated with CBD for at least 12 months at the National Center for Epilepsy (NEC) in Quito-Ecuador.

The inclusion criteria were: 1) Patients of any age group diagnosed with epileptic syndromes catalogued by the International League Against Epilepsy (ILAE) as a Drug-Resistant Epilepsy; 2) Patients that are attended at the National Center for Epilepsy in Quito-Ecuador between 2015 and 2020; 3) Patients that have been treated with Cannabidiol (CBD) at 3% (300 mg/10ml) or at 15% (1500 mg/10ml), with THC 0.02%. Sublingual administration, twice a day daily for at least 12 months as an adjuvant treatment.

2.3. Data Sources

For this study, we used secondary data collected by the health professionals at the NCE throughout the years of follow-up of their patients. We used two anonymized sources of information for the study: hand-written medical records and quality of life surveys.

2.4. Medical Records

The medical records start with a baseline in-depth interview of the patient's caregivers, followed by all the relevant details related to use of medication and CBD, including adverse effects; information that was used for the present study.

2.5. Survey

The health professionals at the NCE applied the CAVE Questionnaire at baseline and several times during follow-up for each patient. This questionnaire measures the impact of epilepsy on quality of life. It was carried out on the patient's relatives or caregivers, considering as a caregiver to whoever was in charge of the patient in their daily care and who, in turn, regularly attended the controls prior to the start of CBD and at the end of 12 months of treatment. The CAVE questionnaire is characterized as being easy and fast to apply, likewise practical and simple to interpret (level of certainty IIb-III-IV, grade of recommendation B-C).

CAVE is a scale designed in Spain, with which the negative impact of epilepsy on various functional aspects of the individual can be identified. Behavior, school attendance, learning, personal autonomy, social relationship, frequency and intensity of seizures and parents' opinions are evaluated. There are eight parameters, the first five of which are semi-objective, two objective items: frequency and intensity of seizures and a subjective item: parental opinion. Each item has a score range of 1 - 5 points ("very bad" to "very good") and the total score is grouped into intervals that are expressed as a qualitative measure of QoL.

The points are distributed in the following manner: 0 - 15 defines a bad QoL, 16 - 23 a moderate QoL, 24 - 31 a good QoL and 32 - 40 a very good QoL. The optimal QoL scores 40 and the worst scores 8.

To validate internal consistency of the test, we applied the test to a larger sample of patients and conducted Cronbach's alpha test.

2.6. Statistical Analysis

Descriptive statistical analysis was carried out in the present study. The statistical software STATA 14.2 was used for the analysis of the data.

For further analysis, Spearman's nonparametric test was used to assess possible correlations between quantitative variables. The value of $p < 0.05$ is calculated as a measure of significance.

2.7. Ethical Concerns

Following Ecuadorian regulations, observational studies based on secondary data do not need an approval by an IRB when information is properly anonymized, as is our case.

3. Results

The general parameters of the patients included in the study are presented in **Table 1**. There were 34 patients included, 15 (44.1%) are female and 19 (55.9%) are male. Out of these, 25 were younger than 10 years old (73.53%) and 9 (26.4%) patients were 10 years old or above. 25 (73.53%) of the patients have an age of onset of epilepsy before 1 and 9 (26.4%) older than 1 year.

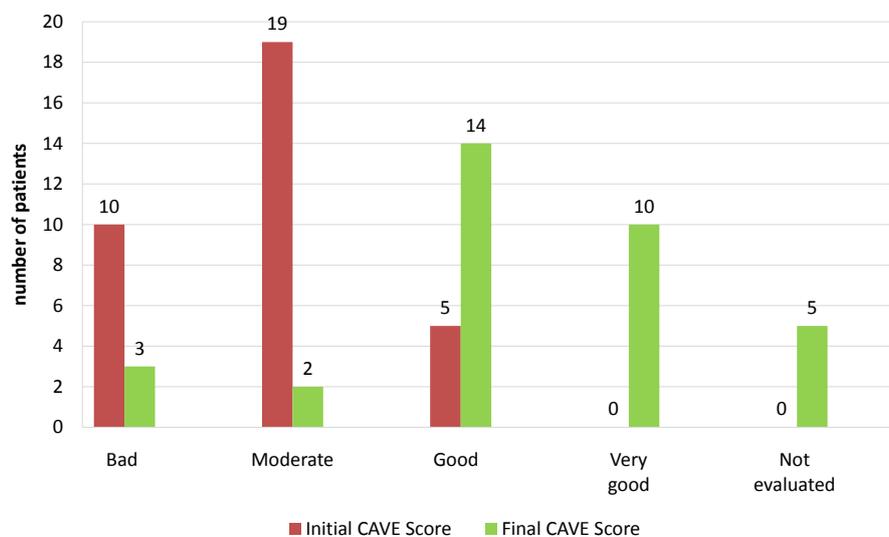
Most patients do not have a family history of epilepsy, but a high proportion of them have pathological data of acquired abnormalities, either prenatal (73.5%), perinatal (55.9%) and/or postnatal history (58.8%). Within the prenatal history, the most relevant difficulties were fetal distress, followed by threatened abortions. Prematurity was the most common perinatal complication, followed by asphyxia. In consequence, the most prevalent comorbidities to epilepsy were psychomotor impairment (70.5%), autism (23.5%), and cerebral palsy (17.6%).

3.1. CAVE Evaluation

The evaluation of the CAVE instrument through Cronbach's Alpha resulted in 0.878, showing high consistency. Through the CAVE scale, we evaluated several parameters and the improvement throughout time. It can be clearly seen that at the beginning of the study the highest percentage of participants presented evaluations with low scores, such as 10 (29.4%) very bad and bad, 19 (55.9%) bad and regular and 5 (14.7%) regular and good. At the beginning of the study, there is no participant who has a high evaluation score. At the end of treatment in the 12-month evaluation, there was a marked change in the improvement of the final evaluation scores. **Figure 1** is a representation of the total change in the final CAVE score that occurred in each of the patients from the start of the study to the end of the study, where a marked improvement can be seen in each of the patients. First of all, very bad and bad evaluations decrease from 10 (29.4%) to 3 (8.8%), bad and regular evaluations start at 19 (55.9%) and decrease to 2 (5.9%).

Table 1. General parameters of patients.

Age (years)	Number of patients (N = 34)	Prenatal Background	Number of patients (N = 34)
0 - 1	4 (11.7%)	Yes	25 (73.5%)
1 - <5	10 (29.4%)	Threatened Abortion	10 (24.41%)
5 - <10	11 (32.3%)	Fetal Distress	11 (32.4%)
≥10	9 (26.4%)	Perinatal Background	
Sex		Yes	19 (55.9%)
Female	15 (44.1%)	Asphyxia	8 (23.5%)
Male	19 (55.9%)	Premature born	9 (26.5%)
Age of Epilepsy Onset		Postnatal Background	
<1 year	25 (73.5%)	Yes	20 (58.8%)
1 - 5 years	7 (20.6%)	Seizures	5 (14.7%)
>5 years	2 (5.9%)	Prolonged Hospitalization	7 (20.6%)
Family History of Epilepsy		Comorbidity	
Yes	14 (41.1%)	Yes	31 (91.17%)
No	20 (58.9%)	Autism	8 (23.5%)
		Cerebral palsy	6 (17.6%)
		Psychomotor impairment	24 (70.58%)
Diagnosis			
Focal symptomatic epilepsy	12 (35.2%)	Doose Syndrome	1 (2.9%)
Familial mioclonic epilepsy	1 (2.9%)	Lennox Gaustat Syndrome	12 (35.2%)
Continuous partial epilepsy	1 (2.9%)	Ohtahara Syndrome	1 (2.9%)
Possible Dravet Syndrome	1 (2.9%)	West Syndrome	5 (14.7%)

**Figure 1.** CAVE score before and after use of CBD.

There is an increase in the regular and good category from 5 (14.7%) to 14 (41.2%), and in good and very good from 0 (0%) to 10 (29.4%).

Figure 2 gives information about the improvement in the CAVE score is notorious and has an impact on the patient’s quality of life. 26 of the 34 patients (76.5%) increased their CAVE score at the end of the study and only 1 (2.9%) decreased their score.

In **Table 2** we describe any improvement that was reported from each patient and resulted in a change in the description based on the scale from a lower category to a higher category. For example, the change from “very bad” to “bad” is

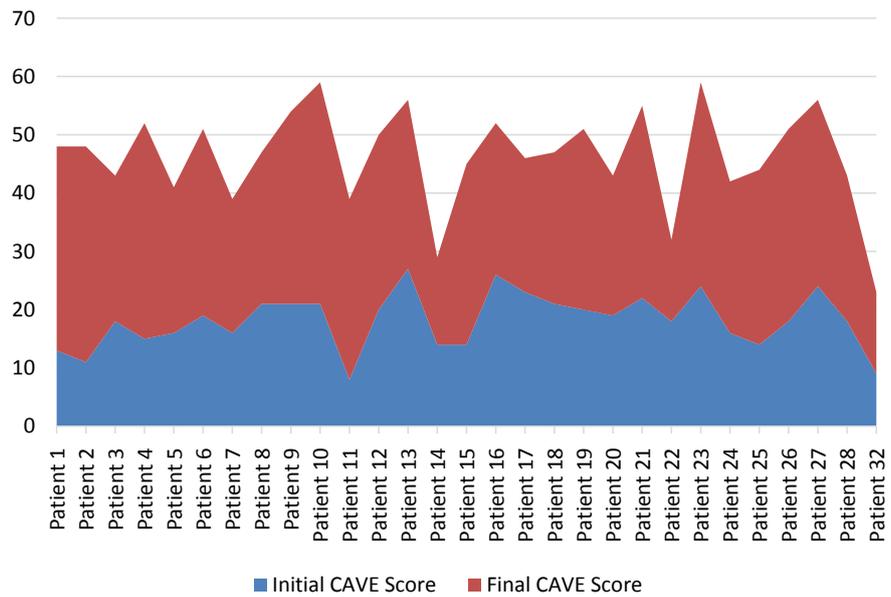


Figure 2. Patients CAVE final score during treatment.

Table 2. CAVE final score at the beginning and the end of the study.

Parameter	Patients Number N = 34											
	Number of categories that patient changes during study											
	Total improvement (n cases (%))	Improves in 1 category (n cases (%))	Improves in 2 categories (n cases (%))	Improves in 3 categories (n cases (%))	Improves in 4 categories (n cases (%))	Does not change (n cases (%))	Decreases (n cases (%))					
Behavior	19 (55.9%)	11 (32.4%)	5 (14.7%)	3 (8.8%)	0 (0%)	7 (20.6%)	3 (8.8%)					
School Attendance	19 (55.9%)	7 (20.6%)	7 (20.6%)	2 (5.9%)	3 (8.8%)	9 (26.5%)	1 (2.9%)					
Learning	17 (50%)	8 (23.5%)	6 (17.6%)	3 (8.8%)	0 (0%)	10 (29.4%)	2 (5.9%)					
Autonomy	11 (32.3%)	6 (17.6%)	3 (8.8%)	2 (5.9%)	0 (0%)	15 (44.1%)	3 (8.8%)					
Social Skills	17 (50%)	10 (29.4%)	4 (11.8%)	1 (2.9%)	2 (5.9%)	9 (26.5%)	3 (8.8%)					
Epileptic seizures frequency	19 (55.9%)	2 (5.9%)	5 (14.7%)	2 (5.9%)	10 (29.4%)	10 (29.4%)	0 (0%)					
Seizures intensity	24 (70.5%)	5 (14.7%)	7 (20.6%)	4 (11.8%)	8 (23.5%)	5 (14.7%)	0 (0%)					
Parents opinion	22 (64.7%)	10 (29.4%)	7 (20.6%)	3 (8.8%)	2 (5.9%)	6 (17.6%)	1 (2.9%)					

registered as an “improvement in one category”. When evaluating each one of the parameters, we can see how the highest percentage of patients has a tendency to improve.

The behavior parameter shows an improvement in 19 patients (55.9%). Regarding school attendance, a total improvement is seen in 19 (55.9%) of the patients. In learning, there is an improvement in 17 (50%) of the patients. In the Autonomy evaluation 11 (32.3%) present an improvement. In the social skills parameter, an improvement is seen in 17 (50%) of the patients.

The frequency of seizures shows an improvement in 19 (55.9%) of the patients. On the other hand, seizures intensity is the parameter that presents the greatest improvement with 24 (70.5%) patients who improved their parameters throughout the study. Finally, the opinion of the parents is the second parameter that presents the greatest improvement with 22 (64.7%) percentage improvement.

When carrying out an analysis between the improvement in the different parameters and the QoL, some relevant results were observed. There is a statistically significant positive correlation between the decrease in the frequency of seizures and the improvement in the final QoL result (correlation coefficient = 0.8412 $p < 0.001$). There is also a statistically significant positive correlation between the decrease in the intensity of the seizures and the improvement in the final QoL result (correlation coefficient = 0.899 $p < 0.001$). Finally, there is a statistically significant positive correlation between the improvement in parental opinion and the improvement in the final quality of life result ($\rho = 0.629$ $p < 0.001$).

3.2. Positive Side Effects

Throughout the study, we were able to observe that besides the decrease in seizures frequency, CBD intake resulted in several positive side effects regarding neurocognitive parameters. **Table 3** represents the improvement in each one of

Table 3. Change in number of categories according to the scale of evaluation of positive side effects on Neurocognitive development during study.

Parameter	Patient number N = 34											
	Total improvement		0 - 1		2 - 3		>3		Does not apply		Reduces a category	
Awareness	30	(88.2%)	15	(44.1%)	14	(41.2%)	1	(2.9%)	3	(8.8%)	1	(2.9%)
Learning	31	(91.2%)	15	(44.1%)	16	(47.1%)	0	(0%)	3	(8.8%)	0	(0%)
Language Skills	31	(91.2%)	14	(41.2%)	17	(50%)	0	(0%)	3	(8.8%)	0	(0%)
Motor skills	31	(91.2%)	18	(52.9%)	13	(38.2%)	0	(0%)	3	(8.8%)	0	(0%)
Sleep	30	(88.2%)	18	(52.9%)	10	(29.4%)	2	(5.9%)	4	(11.8%)	0	(0%)
Conduct	29	(85.3%)	16	(47.1%)	13	(38.2%)	0	(0%)	3	(8.8%)	2	(5.9%)
Affectivity	29	(85.3%)	21	(61.8%)	7	(20.6%)	1	(2.9%)	3	(8.8%)	2	(5.9%)
Aggressiveness	12	(35.3%)	7	(20.6%)	3	(8.8%)	2	(5.9%)	21	(61.8%)	1	(2.9%)

the neurocognitive parameters throughout the study. A clear total improvement is seen in each of the parameters, with learning, language and motor skills improving the most (91.2%), followed by awareness and sleep (88.2%), conduct and affectivity (85.3%) and finally aggression with a 12 patient improvement (35.3%). It is relevant to clarify that aggression was only followed up on patients that presented that trait at baseline, considering that the rest of the caregivers of the participants never reported aggression.

3.3. Negative Side Effects

The total number of patients with negative adverse effects throughout the study is shown in **Figure 3**, observing a decrease in patients with adverse effects from 13 (38.2%) patients after one month of follow up to 4 (11.8%) patients after 12 months.

In the first month, it is seen that the most prevalent adverse effect is drowsiness (11.8%), followed by constipation (8.8%). At 12 months drowsiness remains the most present but has decreased to 2 patients (5.9%) that present it, followed by fatigue and constipation presented in 1 patient (2.9%) each is shown in **Figure 4**.

4. Discussion

The current use of CBD is an important therapeutic option, not only for seizures control, but also for achieving positive changes in the QoL of the patient with epilepsy. Among the participants in our study, we were able to verify the changes in the QoL during a year of treatment with CBD. Prior to starting CBD treatment, 99.5% of patients reported a very poor QoL and, at best, regular, where none of the caregivers classified it as good or very good. Our results are similar to those presented by other authors where the majority of parents of children with epilepsy classify their life and that of their child as bad or very bad [2].

After 12 months of CBD use, changes in the QoL of 76.5% of our participants were very relevant, demonstrating an increase of up to 10 points in the QoL. A similar improvement was previously reported by Rosenberg *et al.*, where 48

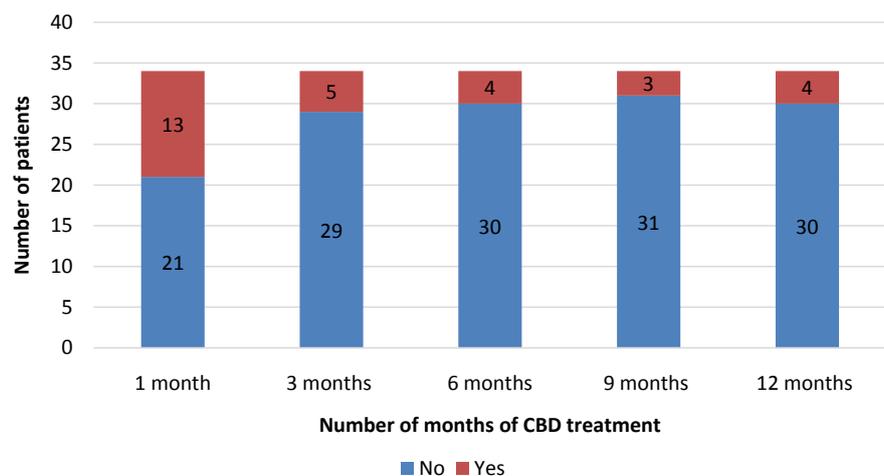


Figure 3. Side effects during CBD treatment.

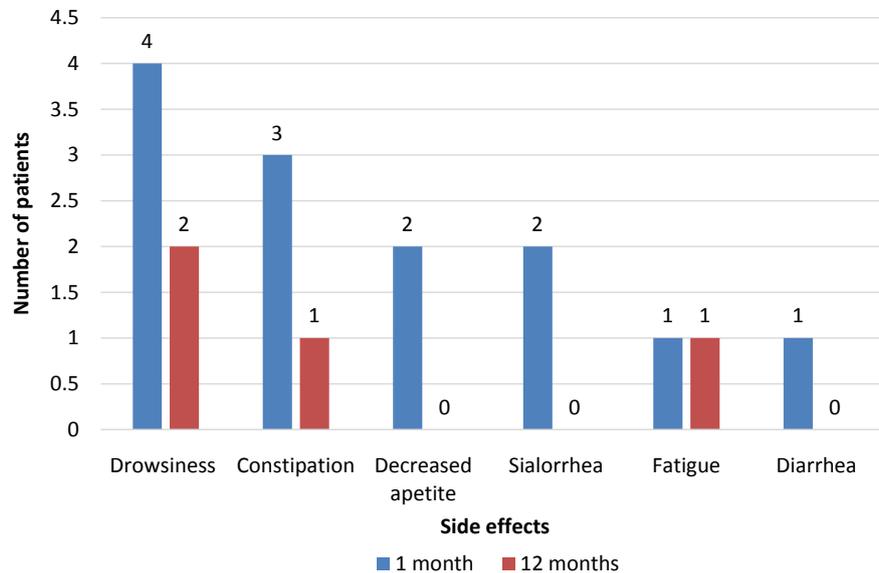


Figure 4. Types of side effect during treatment.

children treated with CBD for 12 weeks, achieved an overall improvement of 8.2 to 9.9 points in the QoL of the patient [4]. When comparing these results with other therapeutic options like epileptic surgery, Sheikh *et al.* reported an increase of up to 5.3 points in the QoL of patients even when seizures control has been achieved [8].

The significant improvement reported in our patients is furtherly understood within the sub items that are assessed in the CAVE survey. The reduction in the frequency of seizures was relevant in 55.9% of patients, of these 29.4% show a very important improvement. Even more interesting is that 70.5% of the patients report a decrease in the intensity of the seizures, which corresponds to the reduction in their frequency and duration. These factors are determining in the perception of a better QoL, a condition that has been widely described with the use of various treatments [3] [9] [10].

However, achieving seizures control is usually not enough to achieve a better QoL, this has also been described in patients undergoing epilepsy surgery that, despite achieving seizures control in the long term, other comorbidities remain, such as symptoms of anxiety and depression, which affect the QoL of the patient and his family [3].

It was interesting to observe how behavior improved in 55.9%, as well as social skills in 50% of patients, both very significant since patients with epilepsy have a 4.7 times greater risk of developing behavioral, relational and emotional problems compared to the general population [10]. In this same way, learning when evaluated by the CAVE scale also improved in 50% of patients, understanding this parameter as the ability to acquire a skill or knowledge. Some participants were able to be schooled after a period of treatment, 55.9% was able to attend special therapeutic or educational activities.

The autonomy parameter improvement of up to 32.3% when evaluated by the

CAVE scale, is important since the analyzed group presented drug-resistant epilepsies that affect development, the majority presented seizures in the first year of life 73.55%, and associated neurological risk factors and comorbidities, which represent a long-term worse prognosis, higher risk of severe psychomotor impairment, and drug resistance [11] [12] [13] [14].

The patient or caregiver's perception of improvement in QoL goes beyond seizures control. The reported changes are associated with what has been called in the literature "positive side effects" [15] [16], seeing an improved ability to learn, communicate and acquire motor skills, followed by a better alertness and better quality of sleep, conduct and affectivity. Even a small group that reported aggressiveness at the beginning of treatment noted significant improvement.

Finally, 64.7% of the parents had a positive opinion regarding CBD treatment, most of the patients do not report negative adverse effects, and if they existed, they were minimal and mainly occurred at the beginning of treatment. Those negative adverse effects were mostly somnolence, constipation and decrease in appetite, being all of these well tolerated, supporting the statement that CBD is generally well tolerated, as is reported by Anciones and Gil-Nagel [17]. Further research would be needed to evaluate if constipation was due to the treatment or to conditions of the patient, considering that it is a rare find when using CBD.

The main limitations in our study are due to the subjectivity that arises from the surveys that are responded by the caregivers, considering answers are due to their perception in most cases. Another important limitation is the relatively reduced sample size, nevertheless, similar studies use even smaller sample sizes.

5. Conclusion

In conclusion, the improvement in QoL achieved with CBD may be independent of seizures control, since it includes changes in cognitive, social and behavioral aspects [4] [16]. These results demonstrate that the same emphasis must be applied not only to achieve adequate seizures control but also to control other aspects of daily life that have a colossal impact on the individual and his family.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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