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Research Article

Efficacy and Tolerability of Add-on Cannabidiol in Pediatric Patients with Drug-Resistant Epilepsy: An Open Exploratory Interventional Study in México

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Abstract

Purpose: To describe the experience of a private neuropediatric clinic on using standardized cannabidiol (CBD) product (RSHO-X™. Medical Marijuana Inc. San Diego, CA, USA), to treat pediatric patients diagnosed with drug-resistant epilepsy (RE) in México.

Methods: Forty-six (46) pediatric patients (age: 1 - 17 years) with severe, drug-resistant epilepsy, who were receiving stable doses of antiepileptic drugs (AED) before study entry. 37 patients were evaluable based on protocol compliance (adherence to treatment and completed control follow-ups at 3, 6, 9 and 12 months). The selected formula contained 5000 mg CBD in 236 mL MCT coconut oil and was free of THC. The initial CBD doses treatment was (1 - 2 mg/kg/day) and progressively titrate the dose up to 5 mg/kg/day during the first 4 weeks to reduce the seizure frequency by 50% or more. The primary efficacy endpoint was the median percentage change in the mean monthly seizure frequency at the end of the study period. The tolerability was evaluated base on the record of the side effects.

Results: The treatment yielded a positive effect on seizure reduction after 3 months. Most of the children 25/37 (67.5%) reported a reduction in seizure frequency; a 100% reduction in 1 (2.2%), more than 80% reduction in 11 (25%), 50% or more in 25 (67.5%) and less than 50% reduction was reported in 12 (27.2%) patients, respectively. Two patients reported an increase in seizures (4.3%), two no improvement (4.3%) and three (6.5%) abandoned with adverse effects dropped out of follow-up before 3 months are not included in this analysis. Adverse reactions occurred in 11/37 (29.7%) patients, with a mild grade in 10 subjects and moderate in 1 subject respectively.

Conclusion: The results of this study on the treatment of CBD (RSHO-X™) oil for drug-resistant epilepsy in children and adolescents are promising with good efficacy and tolerability.

Keywords: *Resistant Epilepsy; Seizures; Pediatric Epilepsy; Cannabidiol*

Abbreviations

CBD: Cannabidiol; RSHO-X: Real Scientific Hemp Oil-X; RE: Resistant Epilepsy; AED: Antiepileptic Drugs; MCT: Medium-chain Triglycerides; THC: Tetrahydrocannabinol; ILAE: International League against Epilepsy; FDA: Food and Drug Administration

Introduction

One-third of the patients with epilepsy are resistant to available antiepileptic drugs. Drug-resistant epilepsy is defined by the ILAE (International League Against Epilepsy) as "a failure of adequate trials of two tolerated and appropriately chosen and used AED schedules

(whether as monotherapies or in combination) to achieve sustained seizure freedom" [1]. A sustained seizure freedom is defined as an absence of epileptic seizure episodes for a period of at least one year or has sporadic seizures separated by a period three times the longest interval between seizures prior to the treatment, whichever is longer. Even though, many new AEDs have been marketed during the past two decades, including ones with novel mechanisms of action, the efficacy profile of these AEDs remains limited and has not substantially reduced the proportion of patients with medically drug-resistant disease [2,3].

Two major substances derived from cannabis or the industrial hemp as oil extracts - a psychoactive tetra-hydrocannabinol (Δ9-THC) and non-psychotropic cannabidiol (CBD) have garnered the most attention based on their abundance in the plant and pronounced anticonvulsant and anti-seizure effects [4,5]. Preclinical studies suggest that naturally occurring cannabinoids (Phytocannabinoids) have anticonvulsant effects that are mediated by the endocannabinoid system [6]. Cannabidiol and cannabidivarin have shown antiseizure was in both *in vivo* and *in vitro* models. In contrast to THC, CBD does not produce euphoric or intrusive psychoactive side effects when used to treat seizures [7]. Studies have shown that the endocannabinoid system may be altered in epilepsy [8] recurrent seizures and the epileptogenesis process decreases the expression of CB1 receptors [9]. Cannabinoids have been proposed as an adjunctive treatment for epilepsy and parents of children with epilepsy report using CBD products [10-12].

In Mexico, a prevalence of epilepsy is reported in 18 cases of 1000 inhabitants (1.2 to 3% of the general population) with a mortality rate of 1.04/100,000 inhabitants in Latin American countries [13]. The remission or reduction of convulsive seizures has been achieved in 75% of cases requiring 2 or more AED and 25-30% of cases meet the criteria for refractory status classification [14]. Obviously, there is a great interest in the development of new drugs and therapeutic approaches that may have antiepileptic properties, particularly those agents that target different receptors or have novel mechanisms of action. In 2018, the U.S. Food and Drug Administration (FDA) has approved a purified CBD formulation (Epidiolex) for children with refractory epilepsy such as Lennox-Gastaut and Dravet syndromes [15].

We conducted this exploratory open-label study at a private neuropediatric clinic to test whether cannabidiol as an add-on treatment to conventional AED would be safe, tolerated, and efficacious in children and young adults with highly treatment-resistant epilepsy in México.

Materials and Methods

Study design and subjects

Between 2015 and 2017, a total of 46 patients were screened and registered in our proposed clinical study database. All subjects were previously examined, and epilepsy disease status assessed by neurological EEG and imaging etiology tests. The caregivers expressed their interest to explore hemp-derived medications as an alternative treatment for refractory epilepsy following an unsuccessful seizure control with the conventional AED treatments. After confirming the presence of drug-resistant epilepsy according to ILAE criteria [1] and obtaining informed consents, Cannabidiol (RSHO-X™. Medical Marijuana Inc. San Diego, CA, USA) was offered by the pediatric neurologist as a compassionate therapeutic in "add on" treatment to patients that have been resistant to two or more medications or treatment such as a ketogenic diet, vagus nerve stimulation (VNS) or surgical procedures. The parents and caregivers also were instructed on the product administration, necessary follow-up with a written record of seizure registry and the warnings of possible side effects. Parents and caregivers were summoned to follow-up consultations. Authorization was obtained by the research and ethics committees of the Health Ministry of Nuevo León State, México.

A group of 37 consecutive, in the office consultation, patients have completed the follow-up of this study analysis. The study data was collected from clinical records obtained through follow-up visits, and consultations of children and adolescents with refractory epilepsy treated with Cannabidiol during the years of 2015 - 2017.

The study patients were divided into six subgroups based on seizures etiology according to ILAE 2017 classification [16]: 1. Structural. 2. Genetics. 3. Infectious. 4. Metabolic. 5. Immune. 6. Unknown.

Clinical study material

In this study we used a single brand of CBD enriched oil - RSHO-X™, that was supplied by HempMeds PX, LLC (San Diego, CA, USA). RSHO-X™ containing 5000 mg CBD in 236 mL MCT coconut oil. RSHO-X™ is made from the non-genetically modified (non-GMO) and certified cultivars of low-THC fiber hemp, grown in Europe. The FDA-approved version of CBD is a refined, isolated and semi-synthetic version of CBD, which confers side effects, including elevated levels of toxic liver enzymes, ALT and AST. CBD oil was extracted from the ground fibrous stalk parts of the hemp plant by supercritical CO_2 fluid technique (SFT) utilizing liquefied CO2 as an extracting solvent. The extraction processes of CBD oil meet the strict requirements of the good manufacturing practice (GMP) in the industry. As a final formulation step, crystalline CBD material was solubilized with the medium-chain triglyceride (MCT) coconut oil. The final formulation was subjected to the rigorous analytical testing to verify the concentration of CBD and verify the absence of THC, terpenes and other cannabinoids, as well as the metals, pesticides, microbes and organic solvents. Although of a botanical source, this not necessarily qualifies as "street drug cannabis" but rather as a dietary supplement version of CBD from botanical sources. The definitive analytical testing was performed by an independent, ISO/IEC-17025 certified analytical laboratory. The COFEPRIS office in Mexico, which is equivalent to the US FDA, has approved the (Permit number 183300EL351597) for human use of this hemp oil and its legal commercialization throughout the country.

Medication and dose

The starting daily dose of RSHO-X™ was calculated based on CBD content and set at 0.5 - 1 mg/kg/day divided into twice-daily dosing. The dose was up-titrated once a week until a meaningful and steady reduction in seizure frequency was achieved or intolerant adverse effects observed. In some cases, the standard medication (AED) dose levels were reduced due to the decrease in seizure frequency or reduced side effects. The final dose used for each patient was defined according to seizure response and side effects.

Seizure record

After the study enrolment patients completed a 3-month pre-cannabidiol, baseline observation period, during which parents or caregivers were asked to record and report the minimum, maximum and average monthly seizure frequencies. After the treatment initiation caregivers recorded the number and type of convulsive seizures during the follow-up period of 3, 6, 9 and 12 months. The appearance of side effects or increment of seizures were recorded as well.

Outcomes

The primary endpoint was to establish the safety and tolerability of cannabidiol and the primary efficacy outcome was a mean percentage change in the monthly frequency of total seizures recorded during the period prior to CBD treatment compared to post CBD treatment recorded at 3, 6, 9 and 12 months.

Evaluation of efficacy

Efficacy was evaluated based on the reduction in the rate of total countable seizures. Seizure reduction was rated according to four levels: aggravation with seizure frequency increase by 25%, no change, slightly decreased seizure frequency (≤ 50%), reduced seizure frequency (≥ 50%), significantly reduced seizure (≥ 80%) and seizure-free (100%). We did not provide data on the efficacy of CBD by type of seizures.

Evaluation of tolerability

The presence of undesirable or adverse events were obtained from medical records from the parents/caregivers. The data evaluated were obtained from each visit during the follow-up period. Each caregiver was requested to respond if during or after treatment they felt

that the patient has suffered or reported one of the following symptoms: sedation, headache, tremor, ataxia, rash, diplopia, fatigue, weight gain or loss, worsening of seizures, agitation, dysarthria, insomnia, vomiting, withdrawal because of side effects, or something else that could be mentioned or observed. Possible effects on behavior and the possibility of inducing or aggravating typical seizures (paradoxical reaction) as it has been previously reported were also evaluated.

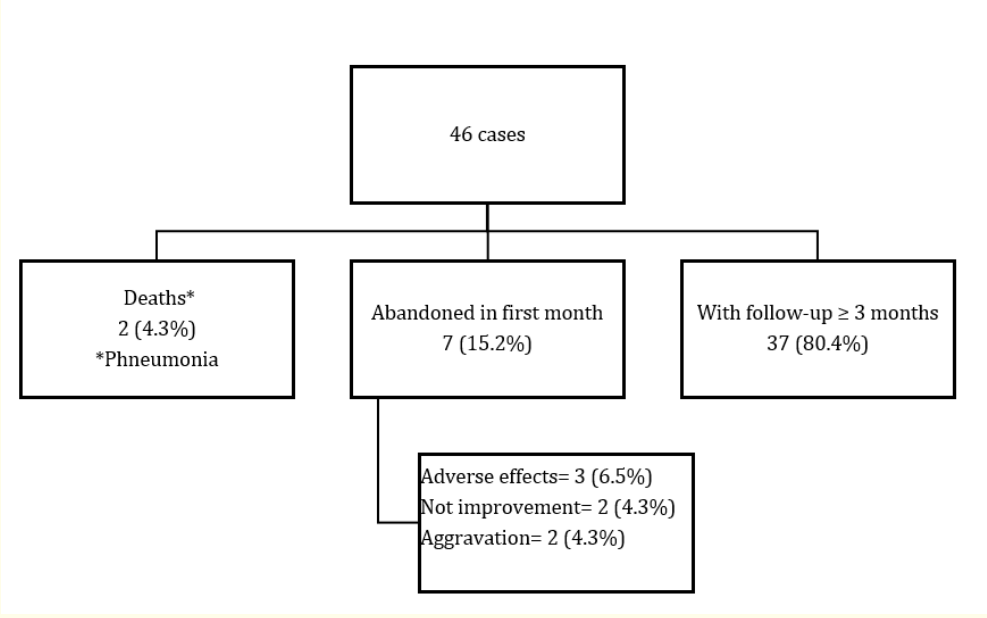
Data analysis

TIBCO Spotfire analytical platform and Microsoft EXCEL (version 14.5.1) were used to analyze the data. Basic descriptive statistics were used to analyze patient population, and safety data, while two-tailed t-Test was used for efficacy analysis and to compare two groups with the same variables. Correlation and Regression data analytical tools were applied to the data to evaluate relationships between different variables. The results were summarized in occurrences and percentages and presented using figures, graphs, and tables. A two-tailed t-test was used for comparison analysis. The results were considered statistically significant when the p-value was < 0.05.

Results and Discussion

A group of 46 patients was enrolled in this exploratory interventional study figure 1. 37 patients completed the treatment minimum period of 3 months. Of the 37 patients who completed the trial, 21 continued treatment post clinical trial: 9 continued treatment up to 6 months, 7 patients up to 9 months and 5 patients up to 12 months.

Figure 1: *Flow chart of consecutive pediatric cases of drug-resistant epilepsy treated with Cannabidiol (CBD).*



The baseline clinical characteristics of patients in the efficacy analysis groups are in table 1. The mean age of patients was 7.1 years (range, 0.5 to 17 years) and 59% were male. Patients had previously tried an average of 4.0 AEDs (range, 1 to 11) and were taking 2.7 AED (range, 0 to 4) during the clinical trial. The most common epilepsy syndromes treated were Lennox Gastaut Syndrome (LGS) and West syndrome (WS). The seizure types are displayed in table 2.

Characteristics	Value (%)
Age (years): mean ± SD range	7.11 ± 4.31
Sex: M/F	22 (59.4)/15 (40.5)
Documented etiology of epilepsy:	Value (%)
Unknown	13 (35.1)
Acquired	4 (10.8)
• Postencephalitic	2
• Hypothalamic hamartoma	1
• Vascular stroke	1
Remote symptomatic	4 (10.8)
• Cytomegalovirus	1
• Hypoxic ischemic encephalopathy	3
Brain dysgenesis	7 (18.9)
• Hypoplasia of corpus callosum	1
• Lissencephaly type 3	1
• Migration disorder	1
• Dandy-Walker	1
• Non-specific dysgenesis	3
Known genetic encephalopathy	9 (24.3)
• Frontal epilepsy AD	2
• Tuberous sclerosis	2
• Cornelia de Lange Syndrome	1
• Rett Syndrome	1
• Landau Kleffner Syndrome	1
• Monosomy of Cr21	1
• Cr14 sat +	1
Epileptic syndromes:	23 (62.1)
• West Syndrome	8 (36.3)
• Lennox-Gastaut Syndrome	14 (60.8)
• Landau-Kleffner Syndrome	1 (4.3)
Age of epilepsy onset (years)	1.42 ± 1.47
Epilepsy duration (years)	6.02 ± 4.19
Type of seizures (ILAE 2017)	
Focal Onset	13 (35.1)
Generalized Onset	22 (59.4)
Unclassified	2 (5.4)
Seizures presentation	
Mixed seizures	28 (75.6)
One type seizure	9 (24.3)
Number of AEDs prior to CBD	4.72± 0.33
Concomitant AEDs post to CBD	2.77 ± 0.18

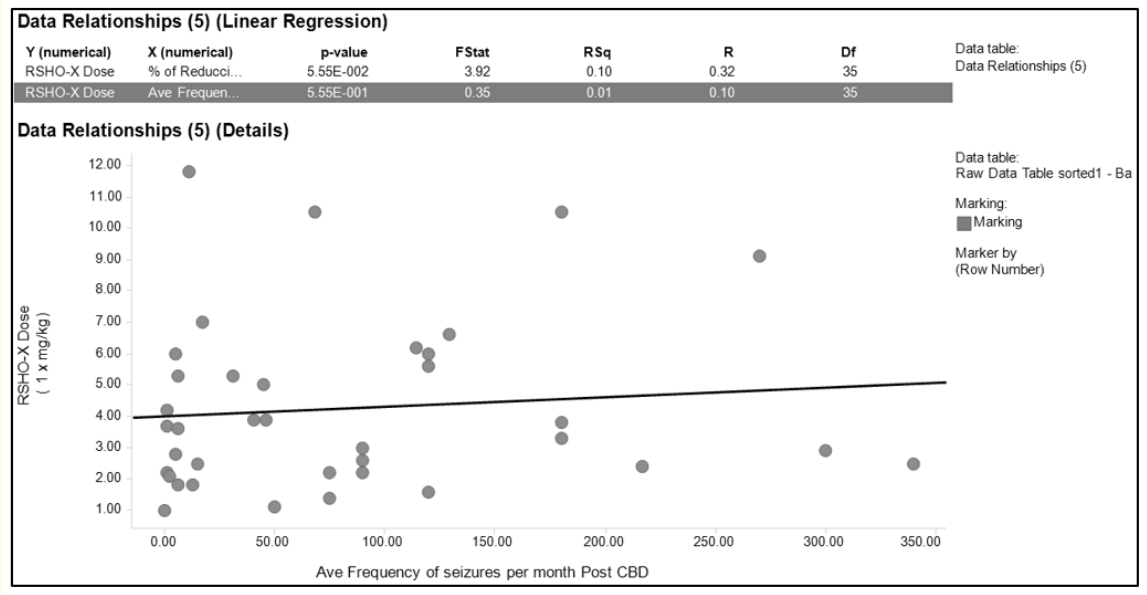
Table 1: *Key baseline characteristics in 37 cases of the trial group.*

Seizure type	Number of subjects	%
Total	**37**	**100**
Epileptic Spasms	22	59.5
Generalized Tonic	17	45.9
Absences Atypical	17	45.9
Focal	10	27.0
Myoclonic	7	18.9
Atonic/Astatic	6	16.2
Generalized Tonic-Clonic	5	13.5
Myoclonic-Astatic	4	10.8
Gelastic	2	5.4
Dystonic	1	2.7
Autonomic	1	2.7
Hypermotor	1	2.7

Table 2: *Seizures type.*

Titration of the dose started with 1 mg/kg/day increments weekly and reached to the maximum daily dose of 11.8 mg/kg in some patients. The average CBD dose at 3 months was 4.35 mg/kg/day (Figure 2).

Figure 2: *Relationship of CBD dose and crisis reduction in 37 cases.*



In regression linear graph it is observable the grouping of the less monthly frequency of seizures in 2 to 4 mg/kg/day CBD doses.

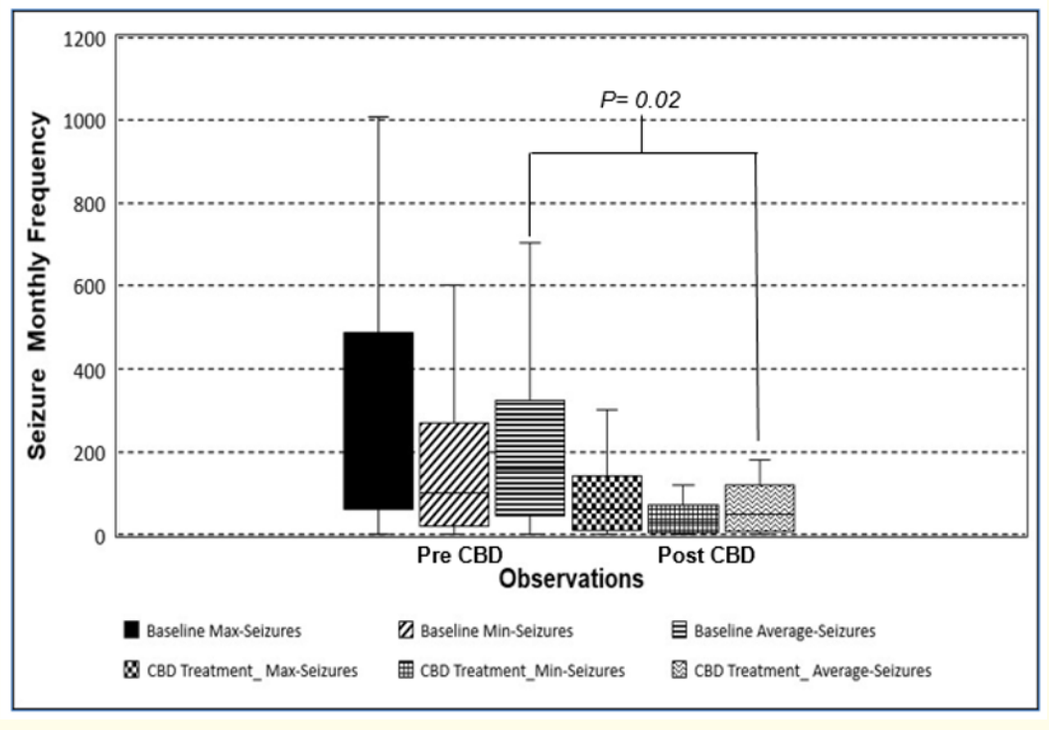
The results of CBD treatment according to seizure etiology are displayed in table 3. In this analysis of the responder rates 25 (67.5%) patients had a reduction of 50% or more in seizure frequency, whereas 11 (25%) had a reduction of 80% or more. One patient (2.2%), with intractable spasms of unknown etiology, became seizure-free at a dosage of 2 mg/kg/d.

% change reduction				
	100%	**≥ 80%**	**> 50%**	**≤ 50%**
Etiology				
Structural	0	5	12	3
Genetics	0	0	3	6
Infectious	0	1	0	0
Metabolic	0	0	0	0
Immune	0	0	0	0
Unknown	1	5	10	3
Responders cases (%)	1 (2.7%)	11 (29.7%)	25 (67.5%)	12 (32.4%)

Table 3: *Percentage change average in monthly seizure frequency of different epilepsy etiology in 37 cases.*

The comparative analysis of minimum, maximum and average seizure frequency values between pre and post-RSHO-X™ treatment periods showed a statistically significant difference (p = 0.02) in reductions of seizures with CBD treatment (Figure 3). In certain cases, the standard medication (AED) dose levels were reduced due to the decrease in seizure frequency or reduced side effects (Table 1). We compared the reduction rate of seizures in cases with and without Clobazam (CLB), the p-value in this comparison was not significative (p = 0.597) (Table 4).

Figure 3: *Monthly frequency of seizures in patients before and after Cannabidiol (RSHO-X™) treatment.*



The difference in the average monthly pre and post-CBD seizures was statistically significant p = 0.02).

% Reduction	CBD only	CBD + CLB	P-value (2tal t-test)
Mean	-74	-62	
Average	-62.58	57.62	
S.D.	30.97	24.62	
			P = 0.597

Table 4*: Compared CBD only vs CBD and Clobazam in % of reduction of seizures. CBD: Cannabidiol, CLB: Clobazam.*

Mild to moderate adverse events were reported by 11/37 (29.7%) patients (Table 5). The most commonly reported adverse events (mild to moderate, and transient) were somnolence, insomnia, appetite changes, increased seizures, anxiety, and irritability.

	Number (%)
Total patients	37 (100)
No side effects	26 (70.3)
Some side effects	11 (29.7)
Insomnia	3 (8.1)
Anxiety	3 (8.1)
Diarrhea	2 (5.4)
Increased appetite	2 (5.4)
Decrease appetite	3 (8.1)
Irritability	1 (2.7)
Drowsiness	1 (2.7)

Table 5*: Side Effects Reported after the Introduction of CBD (RSHO-X™).*

Discussion

In our open-label exploratory study add-on treatment with the isolated cannabidiol (RSHO-X™) led to a clinically meaningful reduction in seizure frequency in many drug-resistant epilepsy children. The high rates of seizure reduction and even the achievement of seizure-free status for one patient suggest the clinically significant efficacy of RSHO-X™. For those patients who achieved seizure-free status or more than 80% reduction in seizure frequency, no previous antiepileptic regimen had been effective during the previous year. However, the major limitations of this study were that it was an open-label and non-controlled study. The issue of the high placebo response and the variable natural history of seizures is especially relevant in pediatric trials of cannabis-derived treatments, thus the results regarding safety and efficacy must be interpreted with caution.

Tzadok., *et al.* [17] reported 74 cases (53.3%) of patients where ≥ a 50% reduction in seizure frequency was achieved using various preparations of CBD, we find similar results (Table 3). Devinsky and co-authors [4,5,11] achieved similar results with Epidiolex, however, the daily CBD dose was several folds higher (20 mg/kg/day) that employed in our clinical trial. The mean CBD dose that led to the significant improvement of seizure control in our patients was estimated at 4.3 mg/kg/day. The results obtained in our exploratory clinical study utilizing non-pharma grade cannabidiol (RSHO-X™) are in good agreement with several clinical trials were treating patients with CBD rich oil demonstrated improvements in seizure frequency with doses far lower than those reported in formal clinical trials of Epidiolex [4,5,17-22].

Particularly, recent meta-analysis [23] of 11 clinical studies with 670 patients demonstrated that 71% of patient's improvement with non-pharma grade cannabidiol (mean daily dose only 6.1 mg/kg/day) compared to 36% improvement achieved with pharmaceutical preparation of Epidiolex with a mean daily dose at 27.1 mg/kg/day [24,25]. In addition, the incidence of mild and severe adverse events was demonstrably higher in pharma-grade purified CBD vs. non-pharma grade CBD rich oil-treated patients, a result that the authors attributed to the lower dose utilized, which was achieved by the synergistic contributions of other entourage compounds [26,27].

In 2018, the FDA has approved and recommended the use of Epidiolex (CBD) exclusively for Lennox Gastaut (LGS) and Dravet Syndromes [19]. However, our results and other studies suggest the possible clinical benefits of CBD treatment in patients with West syndrome (WS) and Landau Kleffner syndrome (LKS). Properly designed randomized clinical trials are needed to explore those possibilities.

The safety and tolerability profile of RSHO-X™ was favorable, with the most patients (70.3%) well tolerating CBD with no observed side effects despite the co-administration of at least of three concomitant AEDs. No serious adverse effects were reported during this study. The most commonly reported side effects were mild and transient that was significantly different from a similar study reported by others previously [4,5,17], where serious adverse events were observed in 20% patients, including status epilepticus and hepatic abnormalities [4,5].

Finally, it should also be underlined that during the follow-up period, we observed the significant decrease in concomitant AED doses from 4.7 (range 1 - 11) to 2.7 (range 0 - 4), which is a definitive advantage in terms of reduced side effects and the overall treatment associated cost. These findings warrant further clinical exploration (safety and efficacy evaluation) with the purpose of further treatment regimen optimization of RSHO-X™ and concomitant AEDs in patients with refractive epilepsy.

Conclusion

The results of this exploratory clinical study suggest a good safety and efficacy profile of RSHO-X™ in pediatric patients with drug-resistant epilepsy of diverse etiology. The main limitation of this study was that it was open-label and exploratory without a control group. Further prospective, well-designed clinical trials using RSHO-X™ are warranted to validate our findings.

Conflict of Interest Declaration

HempMeds PX, LLC had no role in study design, data analysis, data interpretation, or writing of the report, or in the decision to submit the paper for publication. HempMeds PX, LLC provided RSHO-X™ product during the clinical study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. The authors have not received any additional support and/or have not served as paid consultants for the study. None of the authors has any conflict of interest to disclose.

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