Epilepsy & Behavior 95 (2019) 131–136

Contents lists available at ScienceDirect

Epilepsy & Behavior

journal homepage: www.elsevier.com/locate/yebeh

Higher cannabidiol plasma levels are associated with better seizure response following treatment with a pharmaceutical grade cannabidiol

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ARTICLE INFO

Article history:
Received 13 January 2019
Revised 18 March 2019
Accepted 21 March 2019
Available online 29 April 2019

Keywords:
Cannabidiol
Level
Epilepsy
Seizure control
Epidiolex®

ABSTRACT

Objective: The objective of this study was to determine the relationship between cannabidiol (CBD) dose, CBD plasma level, and seizure control in a large open-label single-center study.
Methods: All participants with treatment-refractory epilepsy participating in our expanded access program (EAP) were approached for participation. Highly purified grade CBD (Epidiolex®) dosing was weight-based and could be increased every 2 weeks by 5 mg/kg/day up to a maximum dosage of 50 mg/kg/day depending on tolerance and seizure control. Seizure counts were obtained at each visit with frequency calculated per 2-week periods. Cross-sectional plasma peak levels of CBD were obtained ~4 h after dosing in consecutively presenting patients.
Results: We evaluated 56 adults and 44 children (100 total; 54 female) at two time points — one before initiating CBD and one at the time of CBD plasma level testing. There was a positive linear correlation between CBD dosage (range from 5 to 50 mg/kg/day) and level (range from 7.1–1200 ng/mL) in all participants ($r = 0.640$; $p < 0.001$). The quantile regression model supported the notion of increased CBD levels being associated with improvement in seizure frequency after adjusting for age — specifically, a 100 ng/mL increase in CBD level was associated with approximately two counts reduction in seizure frequency per time period (1.87 96% confidence interval [CI] 0.34–3.39; $p = 0.018$). In participants with the same CBD level, differences in seizure improvement did not depend on age ($p = 0.318$).
Conclusions: In this open-label study, we found evidence of a linear correlation between CBD dosage and plasma levels, and that higher dose/levels are associated with a higher response rate for seizure improvement. Children and adults responded to CBD similarly. However, seizure control response rates suggest children may respond to lower dosages/plasma levels than adults. Findings reported in this study are specific to Epidiolex® and should not be extrapolated to other CBD products.

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1. Introduction

Recently published randomized controlled trials of a pharmaceutical formulation of highly purified cannabidiol (CBD; Epidiolex®) resulted in the approval by the Food and Drug Administration (FDA) for the treatment of seizures associated with the Lennox–Gastaut syndrome (LGS) and the Dravet syndrome (DS) [1–3]. While these regulatory trials addressed two specific pediatric epilepsy syndromes, several open-label studies provided additional evidence for the treatment of other epilepsy syndromes and seizure types in children and adults [4–7]. The results of the randomized controlled trials and the open-label studies of Epidiolex® show consistent results across the studied populations [8]. However, the relationship between CBD dose, plasma level, and seizure control appears to be only partially elucidated.

Recently presented Epidiolex® data indicate that such relationship may exist. In one study derived from the LGS trials, the two dosage levels (10 and 20 mg/kg/day) appeared to have similar treatment effects on median drop seizure reduction [2,9]. However, there was a higher responder rate of >75% and 100% seizure reduction in the higher dosage group. These authors reported trends towards larger seizure reduction with increasing steady-state plasma levels of two major CBD metabolites 7-OH-CBD and 7-COOH-CBD indicating that the drop seizure responder rate was correlated with the exposure of CBD. One study of an artisanal product reported that a higher dosage of CBD (>11 mg/kg/day) combined 20:1 with tetrahydrocannabinol (THC) resulted in a better seizure control than a lower dosage [10].

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https://doi.org/10.1016/j.yebeh.2019.03.042
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Table 1
Demographic data and clinical characteristics of included patients.

Variables	Groups			Test statistic
	Adult	Pediatric	Combined	
	N = 36	N = 44	N = 100	
Age in years	24.0 31.5 45.0 (35.8 ± 14.1)	8.5 12.0 16.0 (12.3 ± 5.3)	14.0 23.0 32.2 (25.5 ± 16.1)	$p < 0.001$[1]
Sex				$\chi_1^2 = 2.9$, $p = 0.087$
Female	46% (26)	64% (28)	54% (54)	
Male	54% (30)	36% (16)	46% (46)	
Baseline seizure freq.	5.4 21.9 50.5 (46.8 ± 128.7)	4.6 12.3 55.3 (97.2 ± 237.7)	5.0 17.1 52.0 (68.9 ± 185.4)	$p = 0.77$
Seizure freq. at CBD level test	2.8 6.0 16.5 (15.6 ± 21.3)	1.2 5.1 26.5 (55.9 ± 149.0)	2.3 5.8 17.4 (33.3 ± 101.5)	$p = 0.49$
Number of AEDs				$p < 0.001$[3]
1	2% (1)	30% (13)	14% (14)	
2	25% (14)	34% (15)	29% (29)	
3	43% (24)	18% (8)	32% (32)	
4	30% (17)	18% (8)	25% (25)	
CBD dose, mg/kg/day	15 25 40 (28 ± 16)	12 20 25 (20 ± 12)	15 20 35 (25 ± 15)	$p = 0.016$[1]
CBD level, ng/mL	72,210,522 (328 ± 292)	54,115,220 (150 ± 124)	59,135,372 (249 ± 249)	$p = 0.005$[1]
CBD exposure out				$\chi_1^2 = 1.6$, $p = 0.21$[2]
Nonresponders	38% (21)	50% (22)	43% (43)	
Responders	62% (35)	50% (22)	57% (57)	
Percent decrease in seizure freq.	18 58 78 (31 ± 136)	12 50 96 (44 ± 108)	17 54 85 (36 ± 108)	$p = 0.74$[1]
Raw decrease in seizure freq.	1.4 10.4 22.7 (31.2 ± 118)	0.8 4.1 24.9 (41.2 ± 112.4)	1.2 7.5 24.1 (35.6 ± 115.1)	$p = 0.35$[1]

abc represents the lower quartile a, the median b, and the upper quartile c for continuous variables. x ± s represents mean ± SD. Number after percentages are frequencies.
[1] Wilcoxon test.
[2] Pearson's chi-square test.
[3] Fisher exact test.

Few studies have reported on the relationship between plasma levels and dosage of CBD. In one of the early observational studies of Epidiolex®, plasma levels ranged from a mean of 388 ng/mL on a dosage of ~20 mg/kg/day to a mean of 450 ng/mL on ~25 mg/kg/day [11]. The randomized controlled dose-ranging study evaluated, among other aspects, the relationship between CBD dosage and the levels of CBD metabolites 6-OH-CBD, 7-OH-CBD, and 7-COOH-CBD to show dose-proportional exposure in the 5, 10, and 20 mg/kg/day range [12]. However, neither of those studies reported on a relationship between seizure response and CBD levels. NCT02324673 (www.clinicaltrials.gov) reported C_{max} plasma levels of synthetic CBD after 10 days of oral dosing in children (mean age of 7.6 years) in response to 10 (119.6 ng/mL), 20 (220.0 ng/mL), or 40 (426.8 ng/mL) mg/kg/day; however, this study did not measure specific seizure responses. Finally, in one study with the data available in a press-release form only, a linear CBD dose/level relationship between two CBD dosages delivered via CBD patch was indicated (www.zynerba.com). However, studies reporting on the entire range of CBD dosing and specifically on the relationship between dose, level, and seizure control have not been reported to date.

The primary goal of the present study was to examine the relationships between the dosage of Epidiolex® and CBD plasma levels in patients with treatment refractory epilepsies (TREs). The secondary goals were to determine whether there was a relationship between improvement in seizure control and CBD dose/CBD plasma levels and whether there were any differences between pediatric and adult cohorts of patients with TREs.

2. Methods

Our study design and methods have been described in detail in our previous publications [7,13]. Hence, we provide only a brief description of the methods with particular attention to the details specific to the present study. Important to note is that while we tried to keep all antiepileptic drugs (AEDs) stable during study participations, adjustments were allowed to be made because of the known interactions with other AEDs [13,14]. Participants signed an institutional review board (IRB)-approved consent form to participate in the parent pediatric and adult University of Alabama at Birmingham (UAB) CBD studies. However, a separate IRB-approved consent form was obtained from participants willing to have plasma CBD levels tested. All of the consecutively and prospectively approached participants agreed to participate.

Table 2
Comparison of all patients' characteristics and clinical measures of responders versus nonresponders.

Variables	N	CBD exposure outcome			Test statistic
		Responders	Nonresponders	Combined	
		N = 57	N = 43	N = 100	
Age in years	100	25.1 ± 15	26 ± 17.6	25.5 ± 16.1	$p = 0.74$[1]
Baseline seizure frequency	100	57.5 ± 138.2	84 ± 234.8	68.9 ± 185.4	$p = 0.38$[1]
Seizure frequency at CBD level	100	10.5 ± 19.2	63.7 ± 148.8	33.3 ± 101.5	$p < 0.001$[1]
CBD dose, mg/kg/day	100	27.1 ± 14.5	21.5 ± 14.2	24.7 ± 14.6	$p = 0.04$[1]
CBD level, ng/mL	100	301.3 ± 278.7	180.6 ± 183.6	249.4 ± 248.7	$p = 0.03$[1]
Raw decrease in seizure frequency	100	47.1 ± 123.7	20.4 ± 102	35.6 ± 115.1	$p < 0.001$[1]
Sex					
Female	54% (31)	53% (23)	54% (54)		$p = 0.93$
Male	46% (26)	47% (20)	46% (46)		
Number of AEDs	100				$p = 0.53$[3]
1	12% (7)	16% (7)	14% (14)		
2	30% (17)	28% (12)	29% (29)		
3	28% (16)	37% (16)	32% (32)		
4	30% (17)	19% (8)	25% (25)		

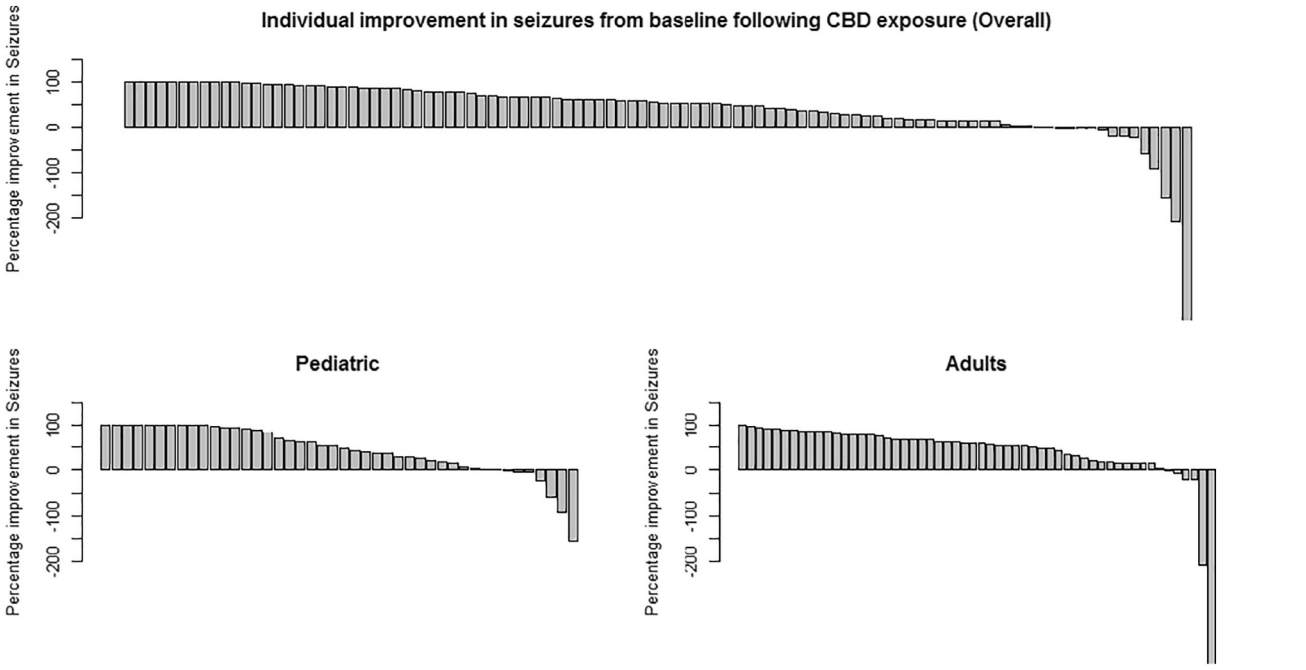

Fig. 1. Percentage change in seizure frequency at first CBD plasma test. Each bar represents each study participant's percentage change in seizures at the time of follow-up visit when CBD level plasma testing was performed compared with baseline. Positive-value bars represent improvement while negative bars shows worsening in seizures. There was a 47-year-old male adult on CBD dosage of 10 mg/kg/day (120 ng/mL plasma level) with exceptional worsening of 922% (from 9 to 92) in seizures, which is truncated in plot because of vertical space.

2.1. Participants

Participants were referred to the parent study either by providers or self-referred if they were able to provide all necessary for enrollment data; all inclusion and exclusion criteria are provided at www.uab.edu/cbd. In order to participate in the current study, the participants had to first enroll in the parent study and already started on a treatment with CBD (Epidiolex®). Once a participant agreed, CBD plasma levels were collected once along with other routine data (not reported here). In each case, the dosage of CBD was stable for at least 14 days, and the level was drawn approximately 4 h after the morning dose. This corresponds to a peak dosage level in all participants that is estimated to be between 2 and 4 h after oral administration [12,15].

2.2. Data collection procedures

All study visits and data collection procedures were conducted in a weekly research clinic. Participants' weight was collected at each visit. The time between study visits was gradually increased up to 12 weeks if dosage adjustments were not made. All participants received an oral formulation of highly-purified CBD in sesame oil (100 mg/mL; Epidiolex®) that was started at 5 mg/kg/day divided between morning and evening dosages that were taken ~12 h apart. At each follow-up visit, the dosage was allowed to be titrated in 5 mg/kg/day increments up to a maximum of 50 mg/kg/day with adjustments made based on seizure response (seizure-free vs. not seizure-free since the last visit) and tolerability (adverse events present vs. absent). In some

Table 3
Comparison of pediatric patient's characteristics and clinical measures of responders to nonresponders.

Variables		CBD exposure outcome			
	N	Nonresponders	Responders	Combined	Test statistic
		N = 22	N = 22	N = 44	
Age in years	44	13 ± 5.3	11.6 ± 5.3	12.3 ± 5.3	$p = 0.38^1$
Baseline Seizure frequency	44	140.2 ± 320.4	54.2 ± 95.9	97.2 ± 237.7	$p = 0.9^2$
Seizure frequency at CBD level	44	102.4 ± 201.1	9.5 ± 22.7	55.9 ± 149	$p < 0.001^2$
CBD dose, mg/kg/day	44	18.6 ± 10.5	22.4 ± 12.4	20.5 ± 11.5	$p = 0.29^2$
CBD level, ng/mL	44	113 ± 72.8	186.3 ± 153.2	149.6 ± 124.2	$p = 0.13^2$
Raw decrease in seizure frequency	44	37.7 ± 140.3	44.7 ± 78.5	41.2 ± 112.4	$p < 0.001^2$
Sex	44				
Female		64% (14)	64% (14)	64% (28)	$p = 1^3$
Male		36% (8)	36% (8)	36% (16)	
Number of AEDs	44				$\chi^2 = 2.68$, $p = 0.44^4$
1		27% (6)	32% (7)	30% (13)	
2		27% (6)	41% (9)	34% (15)	
3		27% (6)	9% (2)	18% (8)	
4		18% (4)	18% (4)	18% (8)	

Data are presented as mean ± SD for continuous variables, raw percentages (frequency) for categorical variables. Test used: [1]*t*-test; [2]Wilcoxon Rank Sum test; [3]Pearson chi-square test; [4]Fisher's exact test.

Table 4
Comparison of adult patient's characteristics and clinical measures of responders to nonresponders.

Variables	N	CBD exposure outcome			
		Responders	Nonresponders	Combined	Test Statistic
		N = 35	N = 21	N = 56	
Age in years	56	33.6 ± 12.7	39.5 ± 15.8	35.8 ± 14.1	p = 0.24[1]
Baseline Seizure frequency	56	59.7 ± 160.6	25.3 ± 30.2	46.8 ± 128.7	p = 0.14[1]
Seizure frequency at CBD level	56	11.1 ± 16.9	23 ± 25.8	15.6 ± 21.3	p = 0.02[1]
CBD dose, mg/kg/day	56	30.1 ± 15	24.5 ± 17.1	28 ± 15.9	p = 0.21[1]
CBD level, ng/mL	56	373.6 ± 315.4	251.4 ± 234.3	327.8 ± 291.6	p = 0.14[1]
Raw decrease in seizure frequency	56	48.6 ± 146.2	2.2 ± 22.8	31.2 ± 118	p < 0.001[1]
Sex					
Female	49% (17)	43% (9)	46% (26)		p = 0.68
Male	51% (18)	57% (12)	54% (30)		
Number of AEDs	56				p = 0.32[3]
1	0% (0)	5% (1)	2% (1)		
2	23% (8)	29% (6)	25% (14)		
3	40% (14)	48% (10)	43% (24)		
4	37% (13)	19% (4)	30% (17)		

Data are presented as mean ± SD for continuous variables, raw percentages (frequency) for categorical variables. Test used: [1]*t*-test; [2]Wilcoxon Rank Sum test; [3]Pearson chi-square test; [4]Fisher's exact test.

patients, the daily dosage of CBD reached 50 mg/kg/day corresponding, in some, to more than 5000 mg/day. The typical dose-limiting adverse events were diarrhea experienced by up to 30% of patients and sedation (14%); other adverse events that were experienced by patients that did not result in dosage adjustments were depression and mood issues (7%; none had suicidal thoughts), and nausea and vomiting (3%); approximately 51% of patients experienced adverse events classified as "other" e.g., dizziness, cold, allergies etc. that were not necessarily related to CBD but were monitored as part of the study. Participants were approached consecutively over approximately 6 months in order to collect data on patients taking various dosages of CBD and the whole array of seizure responses.

2.3. Measures

Plasma levels of CBD were obtained once for each participant. The level was drawn at the same time other laboratory testing was performed to minimize patient discomfort and time commitment. Each lavender top EDTA tube was spun down to separate plasma from cellular elements; plasma was collected and frozen immediately at −20 °C. Pooled samples in batches of 20–30 were shipped to a reference laboratory (NMS Labs, Willow Grove, PA). The CBD level testing at the NMS Labs was performed via high performance liquid chromatography/tandem mass spectrometry (LC–MS/MS) method with results reported in ng/mL with 0.5 ng/mL accuracy (www.nmslabs.com).

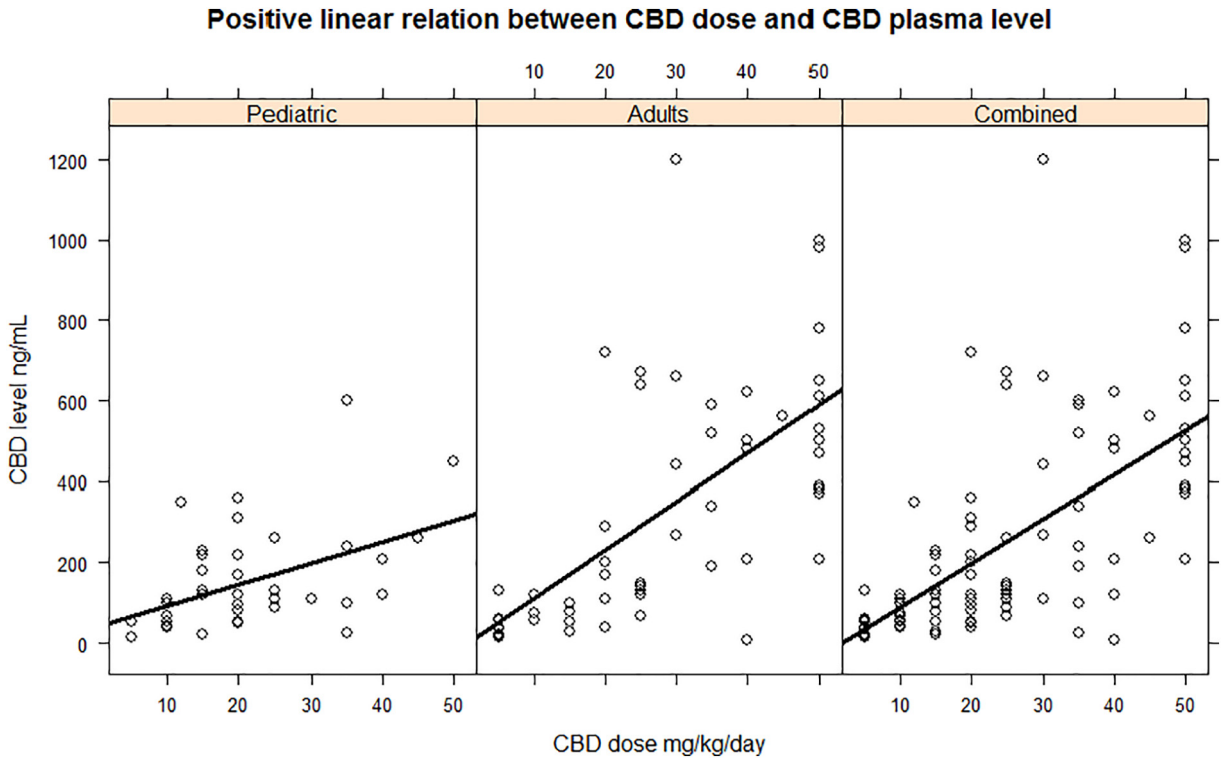

Fig. 2. Relationship between CBD dosage and CBD levels.

At each visit, participants received a neurologic and general medical examination, laboratory testing, and provided seizure diaries of all countable seizures that were reviewed and verified with the participants and/or caregivers by the study physician. Data on baseline seizure frequency (SF) were used to calculate the baseline that later served as a comparator to the on-CBD SF. Seizure frequency was calculated as a number of all seizures per 14 days averaged over the preceding 12 weeks; SF after CBD initiation was calculated between visits and provided also as an average over 14 days. Although we collected data on all seizure types, in many cases, there was no clear demarcation between seizure types and/or participants, caregivers, and providers frequently labeled seizures differently. Thus, the results of analyses based on seizure type would likely be less reliable than analyses based on a total seizure count [7]. With the known limitation of seizure diaries, they were reviewed by the investigator with patient/caregivers for accuracy in reporting [16].

2.4. Data analyses

Patient demographics and clinical measures at baseline were summarized and compared between groups (adult vs. pediatric) using the Wilcoxon's rank sum test for continuous variables and Pearson's chi-squared test for categorical variables. Seizure reduction relative to baseline responder rate of 50% was used to create two groups of responders (≥50% improvement in SF vs. baseline) and nonresponders. To assess whether responders had different baseline characteristics from nonresponders, baseline measures were compared between groups in the combined data and within each group (pediatric vs. adult). Relationship between CBD dosage and CBD plasma level was assessed with Pearson's correlation coefficient. To assess whether increased CBD plasma levels were associated with improved SF the quantile regression model was used to regress changes in SF as a function of age and CBD plasma level (random errors from a similar parametric linear regression model violated the normality and constant variance assumptions). The estimated effect of the CBD plasma level in the quantile regression model was used to establish the relationship between CBD plasma level and seizure improvement at 5% level of significance. All analyses were conducted in SAS and R statistical software. Findings reported in this study are specific to GW's formulation of CBD and should not be extrapolated to other CBD products.

3. Results

Data from 56 adults and 44 children (100 total, 54 female) were included at two time points — one before initiating CBD and one at the time of CBD plasma level testing (Table 1). Overall, there were no differences between the pediatric and adult groups at baseline in sex distribution or baseline SF. At baseline, children were more likely to be on less AEDs than adults ($p < 0.001$). At the time of CBD plasma level testing, the dosage of CBD was higher in the adult group (28 ± 16 vs. 20 ± 12 mg/kg/day; $p = 0.016$), and CBD plasma level was also higher in the adult vs. pediatric group (328 ± 292 vs. 150 ± 124 ng/mL; $p = 0.005$). However, there were no improvements in SF and percentages of responders vs. nonresponders between groups (Table 1). The CBD dosage distribution was between 13 patients taking 5 mg/kg/day and 13 participants taking 50 mg/kg/day. The CBD dosage distribution in the remaining 74 participants was relatively uniform.

Overall, addition of CBD to the treatment regimen resulted in significant improvement in SF (Table 2; Fig. 1) with all participants included in this study reporting either improvement in SF, seizure severity, or both [7]. When comparing responders to nonresponders (Table 2), there were no differences between groups in age or baseline SF. However, responders received higher dosages of CBD (27.1 ± 14.5 vs. 21.5 ± 14.2 mg/kg/day; $p = 0.04$) and had higher CBD plasma levels (301.3 ± 278.7 vs. 180.6 ± 183.6 mg/mL; $p = 0.03$). Participants also had a significant decrease in raw SF and percentage seizure decrease (both $p < 0.001$). There were no differences between groups in number of AEDs (Table 2). Comparisons between responders and nonresponders within the pediatric and adult groups were generally similar to the entire sample (Tables 3 and 4). Further, while there were significant decreases in SF between baseline and CBD plasma level measurement (68.9 ± 185.4 vs. 33.3 ± 101.5; $p < 0.001$), the improvements in SF were similar across arms ($p = 0.35$).

Finally, there was a positive linear correlation between CBD dosage (range 5–50 mg/kg/day) and CBD plasma level (Range 7.1–1200 ng/mL; Fig. 2) in all participants ($\rho = 0.64$, $p < 0.001$). The quantile regression model supported the notion of increased CBD levels being associated with improvement in SF after adjusting for age — specifically, a 100 ng/mL increase in CBD level was associated with approximately two counts reduction in SF per time period (1.87 96%CI 0.34–3.39; $p = 0.018$) while for participants with the same CBD level, differences in seizure improvement did not depend on age ($p = 0.318$).

4. Discussion

In this study, we examined the relationship between the dosage of CBD and plasma CBD levels in a 100 consecutive children and adults enrolled in the UAB expanded access program who were taking a wide range of CBD between 5 and 50 mg/kg/day. We have performed this for a much higher dosing range than in the randomized clinical trials, which evaluated the dosages of 10 or 20 mg/kg/day with the exception of one study that evaluated the relationship between 5, 10, and 20 mg/kg/day CBD dosing and clobazam and *N*-desmethylclobazam levels [12] and one study of synthetic CBD discussed above (NCT02324673; clinicaltrials.gov). In our study, the relationship between the CBD dosage and CBD plasma levels was linear with levels comparable to the levels in the previously reported studies. However, there is substantial variability of the CBD levels possibly reflected by other factors, e.g., food intake status (not monitored specifically in this study), high first-pass metabolism, or individual absorption rates. It is well-recognized that fatty meals can lead to higher secretion of bile acids with subsequent effect on increased drug absorption [17]. Since CBD is highly lipophilic, fatty food may increase its bioavailability. Another reason for the observed variability may be the fact that oral availability of CBD is overall low in humans (<10%), highly variable, and much lower than for other administration routes, such as intranasal or transdermal, where higher exposure to CBD is typically observed [18].

More interesting and important from the clinical point of view is the fact that in our study higher dosages of CBD and higher plasma levels of CBD were associated with overall better seizure control; the relationship was also linear. Splitting participants into >50% responder vs. nonresponder bins resulted in a similar effect being observed. These data provide additional information to the clinician who is prescribing pharmaceutical grade CBD (Epidiolex) to patients with TRE. The data in this study suggest higher levels may be associated with an overall better seizure control; this is similar to data presented in literature from pharmaceutical grade as well as artisanal CBD products [9,10]. While the CBD dosages for children and adults were overall different, the dosage–seizure control relationship was observed in both groups and no differences in response to CBD were observed between pediatric and adult patients in this study. This indicates that children may respond to smaller dosages to achieve the same response as in adults, which is consistent with our previous comparison [7]. Overall, our CBD plasma level data correspond roughly to the data presented previously [11]. However, our analyses expand our understanding of the dosage–level relationship to a much wider range of CBD dosing from 5 to 50 mg/kg/day.

The overall noted seizure improvement in this study is in line with the improvements observed in artisanal and pharmaceutical grade product studies presented in the last few years and is also in agreement with the historical data [8,19]. There is not a question anymore whether

CBD is efficacious for TRE. Rather, the question remains whether it is efficacious alone or in some combination with THC and/or other phytocannabinoids, as all tested formulations have no or very low THC content. There is also the question of whether terpenes, flavonoids, and/or other plant derivatives have an additional effect on seizures, and whether the efficacy of synthetic vs. plant-derived cannabinoids for the treatment of epilepsy and other neurological conditions is comparable [20]. Pure synthetic formulations have entered preclinical and clinical development, and those studies will add additional insights into treatment of refractory epilepsy in children and adults.

Acknowledgments

This study was supported by a grant from Serina Therapeutics, Inc. (JPS), Epidiolex was provided by GW Research Ltd. (Cambridge, United Kingdom), UAB CBD program is supported by Alabama Department of Commerce ("Carly's Law"). Drs. Szaflarski and Bebin are the principal investigators of the adult and pediatric CBD research programs at UAB. UAB CBD studies were registered with www.clinicaltrials.gov under the numbers NCT02695537 and NCT02700412. The results of the study were presented, in part, at the American Epilepsy Society Annual Meeting in New Orleans, LA in December of 2018.

Conflicts of interest

There is no conflict of interest.

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