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Cannabidiol improves frequency and severity of seizures and reduces adverse events in an open-label add-on prospective study

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ABSTRACT

The objective of this study was to characterize the changes in adverse events, seizure severity, and frequency in response to a pharmaceutical formulation of highly purified cannabidiol (CBD; Epidiolex®) in a large, prospective, single-center, open-label study. We initiated CBD in 72 children and 60 adults with treatment-resistant epilepsy (TRE) at 5 mg/kg/day and titrated it up to a maximum dosage of 50 mg/kg/day. At each visit, we monitored treatment adverse events with the adverse events profile (AEP), seizure severity using the Chalfont Seizure Severity Scale (CSSS), and seizure frequency (SF) using seizure calendars. We analyzed data for the enrollment and visits at 12, 24, and 48 weeks. We recorded AEP, CSSS, and SF at each follow-up visit for the weeks preceding the visit (seizures were averaged over 2-week periods). Of the 139 study participants in this ongoing study, at the time of analysis, 132 had 12-week, 88 had 24-week, and 61 had 48-week data. Study retention was 77% at one year. There were no significant differences between participants who contributed all 4 data points and those who contributed 2 or 3 data points in baseline demographic and AEP/SF/CSSS measures. For all participants, AEP decreased between CBD initiation and the 12-week visit (40.8 vs. 33.2; $p < 0.0001$) with stable AEP scores thereafter (all $p \geq 0.14$). Chalfont Seizure Severity Scale scores were 80.7 at baseline, decreasing to 39.2 at 12 weeks ($p < 0.0001$) and stable CSSS thereafter (all $p \geq 0.19$). Bi-weekly SF decreased from a mean of 144.4 at entry to 52.2 at 12 weeks ($p = 0.01$) and remained stable thereafter (all $p \geq 0.65$). Analyses of the pediatric and adult subgroups revealed similar patterns. Most patients were treated with dosages of CBD between 20 and 30 mg/kg/day. For the first time, this prospective, open-label safety study of CBD in TRE provides evidence for significant improvements in AEP, CSSS, and SF at 12 weeks that are sustained over the 48-week duration of treatment.

1. Introduction

The currently available treatments for epilepsy fail to control seizures in 30–40% of patients. Many patients, whether seizure-free or not, report significant adverse events of their treatments that sometimes are felt to be worse than the seizures themselves [1]. There is a need for new treatments that have better efficacy and fewer side effects than the currently available antiseizure drugs (ASDs). There has been great interest in the use of *Cannabis* plant extracts for the treatment of epilepsy [2–4]. Compilation of the anecdotal data and early clinical trials suggests improvement in about 50–60% of patients who took various *Cannabis* extracts for the treatment of treatment-resistant epilepsy (TRE) including those who were treated with purified cannabidiol (CBD) [5]. Observational studies have provided support for developing randomized controlled trials (RCTs) to study the efficacy of a whole *Cannabis* plant or its extract(s) in the management of TREs [5,6]. Several RCTs using a pharmaceutical formulation of highly purified CBD (Epidiolex®) for the treatment of severe childhood epilepsies have been already completed [7–9]. In parallel, several open-label state expanded access programs (EAPs) have been initiated in order to study this formulation of CBD for the management of TRE in patients with other seizure etiologies, e.g., focal onset seizures or those with tuberous sclerosis complex (TSC) [10–12]. In the EAPs, in addition to improved seizure frequency (SF), improved quality of life has been reported in

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patients taking CBD [13]. However, the effects of CBD on seizure severity and adverse events profiles (AEPs) have not been examined to date. The goal of the present add-on study is to assess the safety and efficacy of Epidiolex® in a large sample of children and adults with TRE enrolled in a single-center, open-label EAP safety study, with particular attention to seizure severity and adverse events.

2. Methods

2.1. Participants

The University of Alabama at Birmingham (UAB) CBD program was established to evaluate the safety and efficacy of CBD for the management of TRE. The UAB Institutional Review Board (IRB) approved the EAP under the auspices of "Carly's Law" enacted in 2014 by the Alabama State legislature after appropriate Food and Drug Administration (FDA) and Drug Enforcement Agency (DEA) approvals, and licenses were obtained (www.clinicaltrials.gov numbers NCT02695537 and NCT02700412). Support for the study was provided by the State of Alabama General Funds; GW Research Ltd. provided pharmaceutical grade CBD extract (Epidiolex®) at no cost to the patients. A data safety monitoring board (DSMB) reviewed all clinical data every 6 months with continued approval granted after each meeting.

Providers referred patients to the study based on EAP criteria available at www.uab.edu/cbd; some patients self-referred if they were able to provide all data necessary for enrollment [14,15]. Briefly, participants needed to fulfill the primary inclusion criteria of having a diagnosis of TRE confirmed via video/electroencephalography (EEG) monitoring; failing to achieve seizure freedom with at least 4 trials of different ASDs at an adequate dose including at least one trial of 2 concomitant ASDs (as required by the FDA, patients with a diagnosis of Lennox–Gastaut syndrome or Dravet Syndrome were initially excluded because of preferential enrollment into the randomized clinical trials; once these trials were closed for enrollment, patients with these syndromes were also enrolled (Fig. 1 CONSORT statement)); and at least 4 seizures per month averaged over 3 months. Further inclusion criteria were age > 1 year; if applicable, stable neurostimulator settings and/or ketogenic diet ratio for ≥3 months; documentation of a detailed seizure diary 3 months prior to enrollment and evidence of being able to monitor and document seizures; and State of Alabama residency. The exclusion criteria were history of substance abuse or addiction; use of any medical marijuana or CBD-based product within 30 days of enrollment; history of allergies to CBD or marijuana products or to sesame; felbamate therapy initiation within the 12 months prior to study enrollment; Aspartate Aminotransferase (AST) or Alanine Aminotransferase (ALT) elevation ≥5 times the upper limit of normal levels; hemoglobin < 10 g/dl; hematocrit < 30%; and/or white blood cell count < 2000. Further, doses of ASDs needed to be stable for at least one month prior to enrollment; changes in ASD dosing during study participation was allowed only if ASD interactions or side effects were suspected [14,16]. Once an independent screening evaluation committee approved the patient for study participation, they were scheduled for an initial visit;

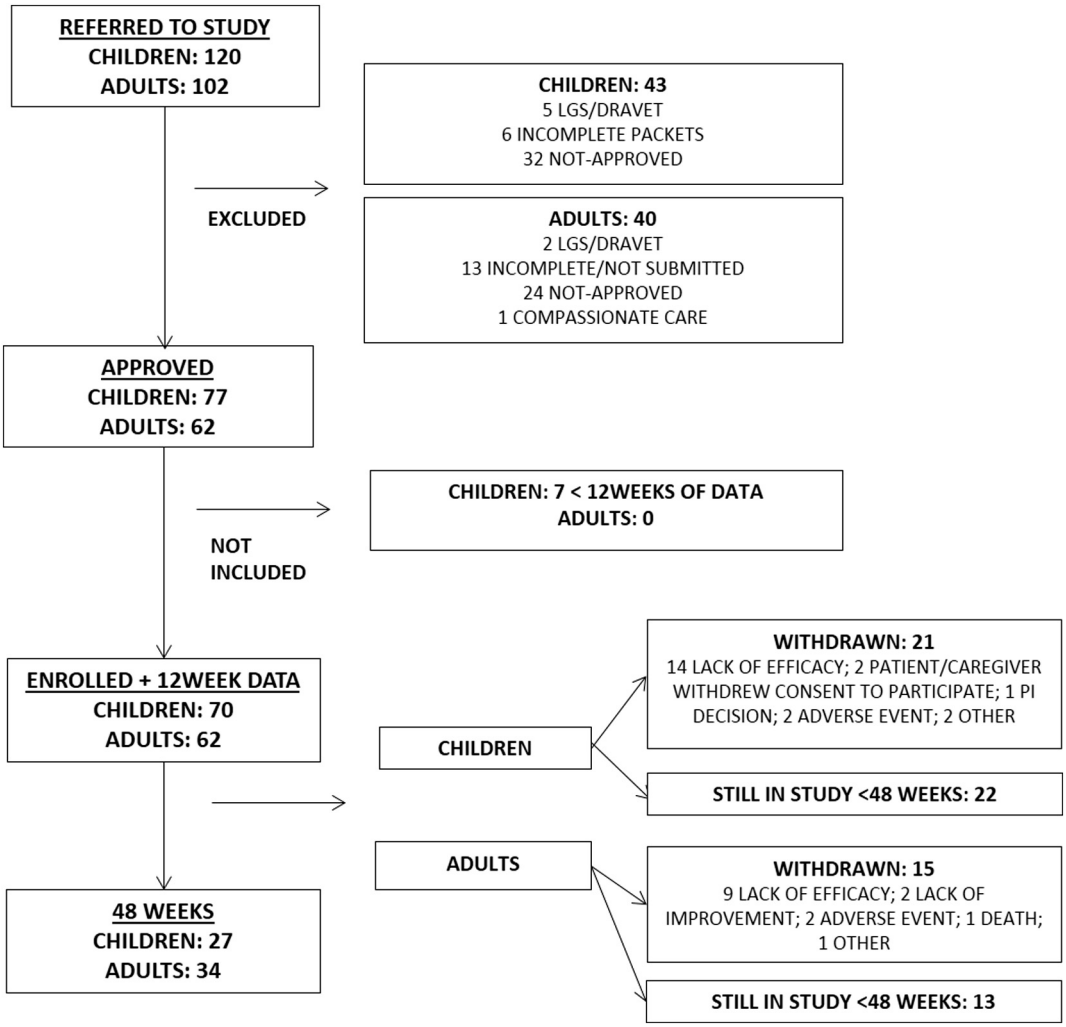

Fig. 1. CONSORT statement.

seizure calendars and necessary laboratory tests were updated at that time.

2.1.1. Data collection procedures

All study visits and data collection procedures were conducted in a weekly research clinic. Participants were evaluated every 2 weeks during active titration of the CBD dose, with the time between appointments gradually increased up to 12 weeks if doses were kept stable. All participants received an oral formulation of highly purified CBD in sesame oil (100 mg/mL; Epidiolex®). Participants were weighed at every clinic visit; CBD was started at 5 mg/kg/day divided between AM and PM taken approximately 12 h apart and typically combined with other ASDs. At each follow-up clinic 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 and tolerability (in some adult patients, daily dosage of CBD reached more than 2000 mg/day). The dosage could be decreased over the phone between clinic visits if there were reports of worsening seizures or side effects; dosage increases were only made in person.

The analyses include data from the first 24 months since study initiation (4/1/2015; Fig. 1 CONSORT statement). One hundred thirty-nine consecutive patients were enrolled prospectively as of the cutoff date for this data analysis (3/31/2017); data on 132 patients were available with at least one of the follow-up visits. Thus, these subjects constitute the study population. We selected for each patient and analyzed data from their required initial visit and visits at 12 ± 2 weeks, 24 ± 4 weeks, and 48 ± 6 weeks. During the study, the time between visits increased up to the maximum of 12 weeks if no adjustments in CBD dosing were made; this flexible follow-up schedule was accounted for in the time points selected for inclusion and analyses. Further, if there were two or more visits that fell into the inclusion period (e.g., two visits for the 48 ± 6 mark at 45 and 49 weeks), the data from the visit closest to the 48-week mark were included in the analyses. All patients entering the study were eligible to be included in this analysis, but their exposure times varied according to date of enrollment. The cohort was analyzed in a pragmatic manner allowing flexible follow-up and mimicking real-world practice to the extent possible in this safety study.

2.2. Measures

At each visit, participants received a neurologic and general medical examination and laboratory testing, provided seizure diaries, and completed study questionnaires including the Chalfont Seizure Severity Scale (CSSS) and AEP [17,18]. All data were collected prospectively using standardized forms and questionnaires. The AEP is a 19-item inventory that assesses ASD adverse effects with higher scores indicating more severe adverse events [19]. Similar to SF, CSSS and AEP baseline data were collected for the 12 weeks preceding study participation while data after CBD initiation were collected specifically for the time between visits. Data on baseline SF were used to calculate the baseline that later served as a comparator to the on-CBD SF. Here, SF 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 as an average over 14 days. While 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. The CSSS is a measure of seizure severity that assesses the components of seizures most disturbing or disruptive to the patient; it has high interrater and test–retest reliability; a change of 10 points or more on CSSS is considered clinically significant [17].

2.3. Data analyses

For the analyses of SF as defined above, descriptive statistics (mean, median, percent change, etc.) were tabulated, and for comparisons, *t*-tests and chi-square tests were used to compare groups with and without follow-up. To compare changes in the three outcome measures, negative binomial regression analyses were conducted using generalized estimating equations' (GEE) analyses for repeated measurement for each participant as a random effect allowing for the varying number of observations per patient and handling the skewness in these count data. The independent variables were study arm (pediatric, adult, and combined) and time point (baseline and 12, 24, and 48 weeks). The least square means of SF were used to assess changes over each of the time points and nominal p-values of 0.05 for their comparisons. For the analyses of seizure severity, the outcome was the total CSSS score (we selected the total CSSS score rather than the CSSS score for the specific seizure type because of the stipulation above regarding potential misclassification of seizure types reported by caregivers or patients). As with frequency, negative binomial, GEE analyses for repeated measurement of each patient were used for the parameter estimation. The least square means of total CSSS scores were compared amongst these study time points as above. Finally, for the analyses of AEP, the outcome was the AEP score. With an offset of visit week at each time point, a negative binomial distribution using GEE for repeated measurement was used in these analyses as well. The least square means of AEP scores were compared amongst all the study points using nominal p-values. Finally, to assess the relationship between CBD dose and percent reduction in SF, mixed model repeated measures were conducted. All analyses were conducted in SAS 9.4 (SAS Institute Inc., Cary, NC).

Table 1
Demographic data for study participants.

	Pediatric participants	Adult participants	Combined	p-Value (between pediatric and adult participants)
N[a]	70	62	132	
Female (%)	37 (53)	33 (53)	70 (53)	0.9662
Age at enrollment (years)	10.1 ± 4.9	30.0 ± 10.8	19.5 ± 12.9	0.0001
Age at seizure onset (years)	2.1 ± 2.8	7.3 ± 8.5	4.5 ± 6.6	0.0001
Epilepsy duration (years)	8.0 ± 4.9	22.8 ± 9.8	14.9 ± 10.6	0.0001
Number of AEDs at enrollment	2.7 ± 1.0	3.0 ± 0.8	2.9 ± 0.9	0.1410
Number of AEDs tried[b]	8.2 ± 2.8	10.1 ± 3.8	9.1 ± 3.4	0.0048
History of epilepsy surgery	16	27	43	0.0114
Seizure type				
Partial	16	41	57	0.0002
Generalized	45	15	60	
Both	9	6	15	
Mean seizure frequency at enrollment	231.8 ± 535.0	45.7 ± 121.5	144.4 ± 407.9	0.0167
Seizure severity at enrollment	78.0 ± 62.8	83.7 ± 49.1	80.7 ± 56.6	0.5715
AEP at enrollment	39.6 ± 9.0	42.1 ± 10.1	40.8 ± 9.5	0.1366

[a] 132 patients had at least two countable visits.
[b] Inclusive of current and previous AEDs.

3. Results

Demographic and clinical characteristics of the participants are included in Table 1 and Fig. 1 (CONSORT statement). All of the 139 patients referred to the study and approved by the independent committee were enrolled; 132 patients (70 pediatric) had at least two data points, one being the baseline, and were included in the present analyses. Differences between pediatric and adult participants were as expected — earlier age at onset and shorter duration of epilepsy were observed in pediatric patients (both $p = 0.0001$). The number of ASDs previously used in adult patients was higher ($p = 0.0048$), which is likely related to a significantly longer duration of epilepsy in adults and greater exposure to various treatments that can diminish in effectiveness over time. Pediatric participants had higher average SF at enrollment ($p = 0.0167$) but similar seizure severity (CSSS) and ASD side effects as measured with AEP. Pediatric patients had epilepsy surgery less often ($p = 0.0114$), which is in agreement with the fact that longer duration of epilepsy results in more patients receiving surgical evaluation and treatment. In addition, many of the pediatric participants had a genetic epilepsy diagnosis or genetic syndrome and/or malformation of cortical development, which is likely reflected in the predominant epilepsy types reported by patients and clinicians (Table 1). Although enrollment for both the pediatric and adult arms of the study was started simultaneously and continued in parallel, we also examined cohort differences and differential dropouts separately. There were no statistically significant differences between those enrolled and, thus, eligible for the 48-week visit and those not eligible. Similarly, within the cohorts, there were 79 individuals eligible for the 48-week visit, and there were no significant differences between the 61 individuals who had a 48-week visit and the 18 individuals who did not (dropouts). There was a slight tendency for the median SF reductions to be smaller, but when changes since the last visit were examined, those not completing the 48-week visit did not exhibit increases in SF over the previous visit, and the numbers were similar for those who had all four visits and those who did not.

Changes in the outcome measures over time are presented in Table 2. Cannabidiol dosing and the number of ASDs used are presented in Table 3. The analysis of AEP indicates significant improvement in the presence/severity of adverse events between the baseline and 12 weeks ($p < 0.0001$) with stable AEPs thereafter, indicating that the adjustments in CBD dose did not result in escalation of adverse events between weeks 12 and 24 ($p = 0.75$) or weeks 24 and 48 ($p = 0.14$). While we have not specifically examined this, it is possible that decreases in ASD doses (e.g., valproic acid (VPA) or clobazam) resulted in this improvement (Table 3 documents the mean number of ASDs

Table 3
Mean dosing of cannabidiol (CBD) and mean number of antiseizure drugs (ASDs) at all four time points (decreases in dose are not captured).

	Baseline	12 weeks	24 weeks	48 weeks
Cannabidiol dosing (mg/kg/day)				
Pediatric	N = 70	N = 69	N = 43	N = 27
		17.5 ± 8.3	19.2 ± 10.1	21.7 ± 8.1
Adult	N = 62	N = 61	N = 45	N = 34
		20.2 ± 7.6	26.6 ± 10.3	32.1 ± 13.4
Combined	N = 132	N = 130	N = 88	N = 61
		18.8 ± 8.0	23.0 ± 10.8	27.5 ± 12.4
Number of ASDs				
Pediatric	N = 70	N = 69	N = 40	N = 26
	2.7 ± 1.0	2.7 ± 1.0	2.6 ± 1.1	2.4 ± 0.9
Adult	N = 62	N = 61	N = 45	N = 34
	3.0 ± 0.8	2.9 ± 0.8	2.8 ± 0.8	2.9 ± 0.8
Combined	N = 132	N = 130	N = 85	N = 60
	2.9 ± 0.9	2.8 ± 0.9	2.7 ± 0.9	2.7 ± 0.9

Table 2
Mean (standard deviation) and median (interquartile range) seizure frequency, seizure severity, and adverse events in study participants (70 pediatric, 62 adult, and 132 combined); seizure frequency includes all countable seizure types.

	Baseline N Mean ± SD Median (IQR)	12 weeks N Mean ± SD Median (IQR)	24 weeks N Mean ± SD Median (IQR)	48 weeks N Mean ± SD Median (IQR)	p-Value*
Seizure frequency (per 2 weeks)					
Pediatric	N = 70	N = 69	N = 43	N = 27	
Mean	231.8 ± 535.0	77.6 ± 147.2	118.1 ± 300.5	71.5 ± 177.25	0.0112
Median	44.8 (10.2,232.2)	23 (45,86.8)	25.7 (3,80.4)	9.2 (4.5,55)	
Adult	N = 62	N = 61	N = 45	N = 34	
Mean	45.7 ± 121.5	24.2 ± 49.0	17.2 ± 21.5	27.1 ± 47.8	0.1161
Median	18 (5,95)	9 (2.5,21)	9.1 (3,23.3)	10.7 (2.2,29.3)	
Combined	N = 132	N = 130	N = 88	N = 61	
Mean	144.4 ± 407.9	52.5 ± 115.1	66.5 ± 215.4	46.7 ± 124.0	0.0101
Median	22 (7,87)	15.8 (3.8,52.3)	12.9 (3,41)	20.4 (3.5,40.8)	
Seizure severity (CSSS)					
Pediatric	N = 70	N = 69	N = 43	N = 27	
Mean	78.0 ± 62.8	45.3 ± 43.1	47.3 ± 44.4	42.8 ± 38.4	<0.0001
Median	64.5 (35.8,106)	36 (3.5,68.5)	35 (15,71)	41 (8.58)	
Adult	N = 62	N = 61	N = 45	N = 34	
Mean	83.7 ± 49.1	32.4 ± 28.7	34.5 ± 34.4	28.1 ± 25.0	<0.0001
Median	75 (50.8,116.3)	27 (10.5,48)	23 (11.5,48.5)	26 (10,49)	
Combined	N = 132	N = 130	N = 88	N = 61	
Mean	80.7 ± 56.6	39.3 ± 37.5	40.7 ± 39.9	34.6 ± 32.2	<0.0001
Median	56.6 (44.3,110.3)	30.5 (8.5,59.5)	32 (13.3,53.3)	29 (8.5,52.8)	
Adverse events (AEP)					
Pediatric	N = 69	N = 68	N = 43	N = 27	
Mean	39.6 ± 9.0	31.2 ± 8.7	29.8 ± 8.4	32.9 ± 9.1	<0.0001
Median	40 (33.5,43.5)	30.5 (23,38)	29 (22,35)	31 (26,43)	
Adult	N = 62	N = 61	N = 45	N = 34	
Mean	42.1 ± 10.1	35.4 ± 10.3	36.0 ± 11.5	35.7 ± 11.3	<0.0001
Median	42.5 (34.8,47)	35 (27,43)	35 (26.5,44)	33 (26,42.5)	
Combined	N = 131	N = 129	N = 88	N = 61	
Mean	40.8 ± 9.5	33.2 ± 9.7	33.0 ± 10.5	34.5 ± 10.4	<0.0001
Median	41 (34,46)	32 (25,39)	31.5 (24.3,39.8)	33 (26,42.5)	

* Mean difference between baseline and 12 week visit; differences between 12, 24, and 48 weeks all $p \geq 0.14$.

Table 4
Changes in seizure frequency in quartiles (responder rates (RR)) over the duration of the study.

	12 weeks	24 weeks	48 weeks
Combined group			
25% RR	66.1%	71.6%	78.7%
50% RR	55.4%	51.2%	63.9%
75% RR	30.8%	26.1%	27.9%
100% RR	6.2%	6.8%	3.3%
Children			
25% RR	63.8%	69.8%	70.4%
50% RR	60.9%	48.8%	63.0%
75% RR	37.7%	32.6%	29.6%
100% RR	8.7%	9.3%	0%
Adults			
25% RR	68.9%	73.3%	85.3%
50% RR	49.2%	53.3%	64.7%
75% RR	23.0%	20.0%	26.5%
100% RR	3.3%	4.4%	5.9%

RR is defined as a percentage of patients who had corresponding decrease in seizure frequency between visits (e.g., at least 25% decrease in seizure frequency).

per patient — there was some decrease in the number of ASDs used overall, but this was not significantly different between time points).

Overall, there was a decrease in the frequency of all seizures by 63.6% ($p = 0.01$) assessed as the mean percent reduction per participant per 2-week period for pediatric and adult groups combined between baseline and 12 weeks. Further, the reductions were sustained with no significant differences, on average, in SF attained between 12 and 24 weeks ($p = 0.79$) and between 24 and 48 weeks ($p = 0.99$) from the repeated measures analysis that takes into account the varying sample sizes to the last visit by each participant. Seizure frequency changes in pediatric and adult patients paralleled the combined data. However, the 47% decrease in SF in adults was nonsignificant ($p = 0.1161$), with the lack of significance likely related to the overall higher variability of response in the adult group. Of importance from these repeated measures models is that the decrease in SF in adults remained stable between weeks 12, 24, and 48, indicating sustained response with the overall decrease ranging between 40.7 and 62.4%. In Table 3, we document that mean CBD doses tended to increase over time in both children and adults, which is consistent with the escalation protocol aiming to provide the most efficacious dose to each patient. While the mean number of other ASDs remained relatively stable across all time points, investigators were allowed to adjust (typically decrease) the doses of other ASDs.

Responder rates (RR) are provided in Table 4. Approximately two-thirds of the participants achieved a ≥25% reduction and about half reported a ≥50% reduction in SF; a few participants were seizure-free. Overall, these rates were generally stable over the duration of study participation. Further, we assessed the effect of CBD dosing on SF in all participants ($N = 132$) and then separately in children and adults. We observed in a mixed effects model with subject treated as a random effect that there was a relationship between CBD dose and the percent reduction in SF. Amongst the individuals who had all 4 visits, the mean dose escalated from 20.85 mg/kg at 12 weeks to 24.4 at 24 weeks and 27.54 at 48 weeks, with higher doses being seen in adults when compared with children at each time point. The estimated coefficient of CBD dose effecting the percent change was −1.55, which is statistically significant (t value = −2.93 $p < 0.004$) and suggests that for every 1 mg/kg increase in CBD dose, there is about a 1.5% linear decrease in the percentage of total SF at baseline. However, because slightly more pediatric cases did not have all 4 visits, adults had slightly higher CBD dosages, and dosages were adjusted to seizure control as well as side effects in this pragmatic study, these results must be interpreted with caution.

Seizure severity data followed a pattern similar to the SF data with one exception: the statistically and clinically significant decrease in CSSS was observed in all groups — pediatric, adult, and combined (Table 2; all $p < 0.0001$). The differences were significant between baseline and 12 weeks, with no significant differences observed between successive time points thereafter (between 12 and 24 weeks, $p = 0.59$ and between 24 and 48 weeks, $p = 0.19$) indicating a sustained response to CBD. Overall, seizure severity improved by approximately 50–60% with participants typically reporting shorter duration of seizures and shorter postictal state; this pattern was similar in children and adults.

4. Discussion

In this prospective, open-label study, we examined the safety and efficacy of pharmaceutical-grade CBD in patients with TRE. In order to examine the safety, we took a somewhat different approach than the previous studies as the safety of pharmaceutical-grade CBD (Epidiolex®) has been confirmed in several observational and randomized controlled studies [7,10,20]. We focused not on reporting of specific side effects but rather analyzed the summary of the AEP data to show that adding CBD to the current ASDs resulted in a statistically and clinically significant decrease in the overall side effects reported by the patients and, maybe more importantly, that the AEP scores remained stable thereafter despite further increases in CBD dosing and decreases in other ASDs. Of note is that only 2 participants in the pediatric and 2 in the adult portions of the study withdrew because of adverse events alone (Fig. 1). We, of course, need to be cautious in our interpretation of the results in this open-label study. Since these participants had to meet specific SF criteria to qualify to participate in the study, this could have led to a bias towards overcounting or overreporting of seizures and overall dissatisfaction with current therapies during the baseline period. Thus, the declines over time may be partly influenced by the expectation of efficacy and regression to the mean that are so common in such studies [21]. Nevertheless, as placebo effects generally dissipate over time, the sustained response in all measures observed over the time points suggests effectiveness of CBD for the treatment of seizures. We also note that, as in all cohort studies, a healthy cohort effect can be occurring here. Although dropouts were few (23/36 of the withdrawn participants did so because of lack of efficacy; Fig. 1), the dropouts presumably are the participants not doing as well, and thus, this too may contribute to the stability in SF, CSSS, and AEP over time.

An additional new finding is the result of seizure severity data (CSSS) analyses. Here again, we observe a concomitant decrease in seizure severity by 50–60% (or 30–40 points) between the baseline and 12 weeks with stable subsequent CSSS scores. Subsequent analyses revealed that the improvements in SF and CSSS were parallel to each other, further adding to the overall improvements experienced by the patients. Since our pragmatic design allowed adjustments of other ASDs, some of the higher CBD dosing in this study when compared with the doses utilized in the RCTs may be related to patients wanting to decrease other, ineffective ASDs similar to observations in other EAP studies [12]. Seizure severity also improved in parallel to the improvements in AEP and SF. Of importance is that an improvement of 10 points or more on the CSSS scale is clinically significant [17]. Since the improvements between baseline and 12-week visits were in a 30- to 40-point range for each group, they are clearly not only statistically but also clinically significant for the group as a whole. Further, these improvements were sustained over the duration of the study.

The AEP is a validated measure that assesses the overall adverse events experienced by the patient; it has been shown that the use of this instrument affects clinical decision-making and that the decreases in AEP are reflected in improvements in quality of life [19,22]. However, more interesting is the fact that we observed an improvement in AEP while the number of existing ASDs remained relatively stable, potentially indicating that CBD may have positive effects on mood, behavior, and overall well-being of the patients. These improvements could also be related to the decreases in the dosing of other ASDs that was done

in parallel to the increases in CBD in some patients at the discretion of the managing provider [12]. Overall, the improvements in AEP are certainly in line with some of the reports that indicated improvements in overall behavior in response to *Cannabis* products [23] and the central effects of CBD on emotion circuits (see [24] for a detailed review). On the other hand, this could be partially a placebo response related to expectation of efficacy as such an effect has been observed in a substantial number of patients enrolled in *Cannabis* epilepsy studies [25] and in studies of patients with other neurological disorders [21]. However, if this was a placebo response, we would not expect it to remain sustained for 48 weeks and be present for all measures (see below), especially SF, which is the case here. Thus, our AEP data suggest that the overall effect of CBD may extend beyond seizure control [13,23].

We also observed a substantial decrease in SF in the combined and pediatric arms and a trend towards decreasing frequency in the adult arm between the prospective baseline and 12 weeks, with further maintenance of the response at 24 and 48 weeks after CBD initiation. While the improvements in SF in adults were not statistically significant, the mean improvement of 47% is potentially clinically meaningful. However, more interesting is the fact that the SF after the first 12 weeks remained stable despite slight decreases in the mean number of ASDs between time points (Table 3). This is consistent with sustained response to CBD in SF over time and extends the results of the available observational trials and RCTs that were limited to reporting a response at 12–14 weeks [7,9,10]. In the combined pediatric and adult groups, as well as the pediatric only group, the decreases in SF between the baseline and 12 weeks were significant, supporting the notion that other factors (e.g., type of epilepsy, other ASDs, longer durations of TRE, and/or smaller sample size) may have played a role in the lack of significance observed in adults. These findings have led us to plan more detailed analyses that will look specifically at each participant's epilepsy diagnosis, seizure types, ASD combination with CBD, and the presence of underlying genetic diagnoses.

This study, as with all open-label studies, is not without limitations. These include potential bias for patient selection; flexible dosing schedule; patient, caregiver, and provider knowledge of the prescribed product; regression to the mean; and expectation of efficacy and variability in epilepsy diagnosis (e.g., genetic vs. other causes). Over- or underreporting of seizures is also a possibility that may reflect patients' or caregivers' desires to qualify or remain in the study, respectively. Nevertheless, the results are in line with the results of randomized controlled studies and in support of the use of CBD in TRE.

5. Conclusions

The results of this open-label safety study indicate significant improvements in CSSS, AEP, and SF at 12 weeks, with response maintained over the 48-week duration of therapy. The results are particularly interesting since rather than enrolling patients with a specific syndromic diagnosis of (e.g., Lennox-Gastaut Syndrome (LGS)), we enrolled patients of all ages with various TRE types.

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Disclosure

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