



Contents lists available at ScienceDirect

Epilepsy & Behavior

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

Open-label use of Highly* purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes

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ARTICLE INFO

Article history:

Received 2 March 2018

Revised 30 April 2018

Accepted 9 May 2018

Available online xxxx

Keywords:

Cannabidiol

Aicardi syndrome

CDKL5 deficiency disorder

Dup15q syndrome

Doose syndrome

ABSTRACT

Objective: We studied our collective open-label, compassionate use experience in using cannabidiol (CBD) to treat epilepsy in patients with CDKL5 deficiency disorder and Aicardi, Doose, and Dup15q syndromes.

Methods: We included patients aged 1–30 years with severe childhood-onset epilepsy who received CBD for ≥10 weeks as part of multiple investigator-initiated expanded access or state access programs for a compassionate prospective interventional study: CDKL5 deficiency disorder (n = 20), Aicardi syndrome (n = 19), Dup15q syndrome (n = 8), and Doose syndrome (n = 8). These patients were treated at 11 institutions from January 2014 to December 2016.

Results: The percent change in median convulsive seizure frequency for all patients taking CBD in the efficacy group decreased from baseline [n = 46] to week 12 (51.4% [n = 35], interquartile range (IQR): 9–85%) and week 48 (59.1% [n = 27], IQR: 14–86%). There was a significant difference between the percent changes in monthly convulsive seizure frequency during baseline and week 12, $\chi^2(2) = 22.9$, $p = 0.00001$, with no difference in seizure percent change between weeks 12 and 48. Of the 55 patients in the safety group, 15 (27%) withdrew from extended observation by week 144: 4 due to adverse effects, 9 due to lack of efficacy, 1 withdrew consent, and 1 was lost to follow-up.

Significance: This open-label drug trial provides class III evidence for the long-term safety and efficacy of CBD administration in patients with treatment-resistant epilepsy (TRE) associated with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. Adjuvant therapy with CBD showed similar safety and efficacy for these four syndromes as reported in a diverse population of TRE etiologies. This study extended analysis of the prior report from 12 weeks to 48 weeks of efficacy data and suggested that placebo-controlled randomized trials should be conducted to formally assess the safety and efficacy of CBD in these epileptic encephalopathies.

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<https://doi.org/10.1016/j.yebeh.2018.05.013>

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Please cite this article as: Devinsky O, et al, Open-label use of Highly* purified CBD (Epidiolex®) in patients with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose synd., Epilepsy Behav (2018), <https://doi.org/10.1016/j.yebeh.2018.05.013>

1. Introduction

Severe epilepsies of childhood are associated with devastating neurodevelopmental delays. When cognitive, behavioral, and sensorimotor impairments exceed what is predicted from the underlying pathology, it is postulated that epileptic activity may directly impair function, i.e., epileptic encephalopathy (EE) [1]. Most EEs are associated with treatment resistant epilepsy (TRE), high medication burden, disabling comorbidities including cognitive slowing and/or regression, and increased mortality due to sudden unexpected death in epilepsy (SUDEP), status epilepticus, and drowning [2].

Common causes of EE include genetic epilepsies such as CDKL5 deficiency disorder and Dravet (DS), Dup15q, Aicardi, and Doose syndromes [1–6]. Seizures in these disorders are often resistant to available medication, dietary, or neurostimulation therapies. In many cases, existing therapies can cause or exacerbate cognitive, psychiatric, and motor disorders in addition to adverse systemic effects. There is a desperate need for safer and more effective antiseizure therapies for the EEs.

While recent randomized, placebo-controlled trials (RPCT) have demonstrated that an adjunctive oral, pharmaceutical formulation of Highly* purified CBD is a tolerable and effective treatment of two severe childhood-onset epilepsies, DS and Lennox–Gastaut syndrome (LGS) [5,6], prior open-label studies [7], anecdotal reports [8,9], and data from animal models [10,11] suggest that CBD may have antiseizure effects in a broad range of epilepsy syndromes and etiologies. Open-label studies found that CBD is effective in treating seizures associated with tuberous sclerosis and in febrile infection-related epilepsy syndrome (FIRES) [12,13]. However, a recent phase II RPCT of CBD for refractory focal epilepsy in adults using transdermal synthetic CBD failed to show a significant reduction in seizures in either the high-dosage or low-dosage groups over 12 weeks [14]. Systemic exposures to CBD in this study have not yet been reported. These discordant findings suggest that the efficacy of CBD may vary by seizure type, epilepsy syndrome, age, or route of administration [15]. Data from the open-label experience [7,12,13] with the oral, pharmaceutical formulation of CBD accurately predicted efficacy results (although no placebo data were available) of the subsequent phase III RPCT [6,20].

Beyond RPCTs for LGS and DS, there are limited data on other epilepsy syndromes, including many of the severe genetic epilepsies. We reviewed our collective open-label experience in using CBD to treat epilepsy in patients with CDKL5 deficiency disorder and Doose, Dup15q, and Aicardi syndromes. These groups were selected because the number of subjects studied in the open-label study was sufficiently large to justify subgroup analysis. There are currently no FDA-approved medications specifically for epilepsy occurring in patients with any of these syndromes.

2. Methods

Children and young adults with severe childhood-onset epilepsy who received CBD as part of multiple investigator-initiated expanded access programs or state access programs for compassionate use were enrolled in a prospective interventional study [7]. We identified cases of CDKL5 deficiency disorder ($n = 20$, 36%), Aicardi syndrome ($n = 19$, 35%), Dup15q syndrome ($n = 8$, 15%), and Doose syndrome ($n = 8$, 15%) at NYU Langone Medical Center, Massachusetts General Hospital, Lurie Children's Hospital, Pediatric and Adolescent Neurodevelopmental Associates (Atlanta, GA), Texas Children's Hospital, University of Utah Medical Center/Primary Children's Hospital, Wake Forest School of Medicine, and Nationwide Children's Hospital from January 2014 to December 2016. Concordant data were included from sites at the University of Iowa Hospitals and Clinics and University of Alabama in this extension. Patients treated included a group participating in the previous open-label CBD EAP analysis exploring CBD's antiseizure effects [7] as well as additional patients who began treatment after the prior study's enrollment cutoff,

with all efficacy analysis including last observation carried forward (LOCF) through 48 weeks of follow-up and safety analysis through 144 weeks of extended follow-up.

After parents or patients provided informed consent and/or assent, the patients entered a four-week baseline period when parents/caregivers kept prospective seizure diaries. They were asked to focus on countable, discrete seizures with a sustained (>3 s) motor component (henceforth referred to as "convulsive seizures"). These include tonic-clonic, tonic, clonic, atonic, and focal seizures with prominent motor features. Although myoclonic, absence and nonmotor focal seizures with impaired awareness were counted, they were not considered part of the primary outcome measure. Convulsive motor seizures can be more reliably counted by observers than more subjective, nonconvulsive (impaired awareness) or transient (myoclonic seizure/jerk), phenomena in a child with an EE. We were concerned about potential parental bias based on their desire for benefit as well as the media attention and parental desire to be on CBD so we believe convulsive seizures to be the most objective measure for treatment effect.

Patients received a plant-derived pharmaceutical formulation of Highly* purified CBD, trade name Epidiolex (GW Pharmaceuticals, UK), in either a 25 mg or 100 mg per mL sesame oil-based solution. Cannabidiol at 5 mg/kg/day administered in two divided dosages was added to the baseline antiseizure drug regimen and then titrated every two weeks or less, as appropriate, by 2–10 mg/kg/day increments until intolerance or a maximum dosage of 25 mg/kg/day. At some sites, IRB and FDA allowed an increase to a maximum dosage of 50 mg/kg/day. For the first three months of CBD therapy, efforts were made to keep concomitant antiseizure drug dosages constant. In some cases, however, sedation due to elevations in concomitant antiseizure drug levels following the addition of CBD led to decreases in those drugs as clinically indicated. All seizures were recorded on paper diaries and reviewed by the study team at each visit. Tolerability and adverse effects were assessed every 2 weeks. In addition, we recorded use of rescue medications, episodes of status epilepticus, and emergency room visits/hospitalizations. Rescue medication use and organ function analysis was not performed because of lack of robust and consistent data.

The primary efficacy outcome measure was median percent change from baseline in monthly seizure frequency at the 12th and 48th week of the observation period for convulsive seizures, calculated as follows:

Percent change in seizure frequency

$$= \frac{[\text{median monthly seizures (12 weeks)} - \text{median monthly seizures (baseline)}]}{\text{median monthly seizures (baseline)}} \times 100\%.$$

Percent change in mean monthly frequency for all seizures recorded by parents and each subtype was also calculated (secondary measures). Comparison between groups for percent change at each time point and for percent change over time was done using a Friedman test for non-parametric repeated measures. Those who did not characteristically exhibit convulsive seizures were not included in primary outcome analysis as change in convulsive seizure was the primary efficacy measurement. Patients whose participation was discontinued before, or had not yet reached the analysis endpoint of 48 weeks, or patients who did not report seizures for a scheduled interval were accounted for by a last-observation carried-forward analysis. As another secondary analysis, we assessed responders at each time period, defined as subjects whose mean reduction in monthly convulsive seizure frequency was 50% or greater. Responder rate was calculated from individual patient percent reductions. Statistics were performed using SPSS (Cary, NC).

The study was approved by the IRB at each institution.

3. Results

We analyzed data from 55 patients enrolled in our collective open-label use study between the dates of January 2014 and December 2016, with 55 (100%) in the safety group and 50 (91%) in the efficacy

group. Four patients were enrolled but did not characteristically exhibit any convulsive seizures, leaving 46 (92%) of those patients receiving CBD with all inclusion criteria for the primary efficacy measurements.

The patients with Aicardi syndrome ($n = 17$) and CDKL5 deficiency disorder ($n = 18$) in the efficacy arm were all female, consistent with the X-linked dominant inheritance pattern [16,19]. Most participants (92%) were under 18, and at baseline, the number of concomitant anti-seizure drugs was often 2–3, with 90% (45/50) of the participants in the efficacy group on more than 1 antiseizure drug (Table 1a).

3.1. CBD dosages

The mean maximum CBD dosage across efficacy participants was 29.6 mg/kg/day ($SD = 12.2$ [$n = 50$]) and 29.4 ($SD = 13.2$ [$n = 55$]) for the safety group. In the safety arm, 24 (43.6%) experienced a reduction in CBD dosage of ≥ 10 mg/kg/day at some point during the study. By week 48, the mean dosage of CBD was 28.48 mg/kg/day ($SD = 11.1$ [$n = 27$]) in the efficacy group.

The average CBD dosage for all patients in the pooled safety group by the first check-in at weeks 2, 12, and 48 was 8.4 ($SD = 2.2$), 22.1 ($SD = 10.1$), and 28.9 mg/kg/day ($SD = 11.2$), respectively. This was consistent across all subgroups, with the Aicardi subgroup receiving mean dosages of 8.1 ($SD = 2.3$), 26.7 ($SD = 12.7$), and 32.0 mg/kg/day ($SD = 12.3$). The CDKL5 subgroup received mean dosages of 8.3 ($SD = 2.6$), 18.2 ($SD = 7.0$), and 26.2 mg/kg/day ($SD = 10.1$). The Dup15 subgroup had averages of 8.7 ($SD = 1.9$), 18.4 ($SD = 7.4$), and 29.2 mg/kg/day ($SD = 9.1$), and the Doose subgroup had similar levels at 8.8 ($SD = 2.5$), 22.0 ($SD = 5.3$), and 27.5 mg/kg/day ($SD = 15.5$). This indicates that although the dosages overall increased between visits, there were no differences between dosages by subgroup epileptic etiology (Fig. 1).

3.2. Baseline monthly seizure activity

The median number of convulsive seizures reported during the 28-day observation period for patients with Aicardi syndrome was 46.7 seizures ($n = 14$, interquartile range (IQR): 18–74). Total seizure frequency, defined as both convulsive and nonconvulsive seizures reported in patients with Aicardi syndrome, was 56.7 ($n = 17$, IQR: 18–109). Patients with CDKL5 deficiency disorder had a reported median baseline convulsive seizure frequency of 80.8 seizures over 28 days ($n = 17$, IQR: 28–158) and a median total seizure frequency of 98.6 seizures ($n = 18$, IQR: 52–233). Patients with Doose syndrome had a median convulsive seizure frequency of 60.8 ($n = 7$, IQR: 26–126) and a total seizure frequency of 64.7 ($n = 7$, IQR: 26–127). Patients with the Dup15q variant had a reported median convulsive seizure baseline frequency of 118.5

($n = 8$, IQR: 32–231) and a total seizure frequency of 149.1 ($n = 8$, IQR: 57–313). The overall median baseline seizure frequency per 28 days for all patients with CDKL5 deficiency disorder and Doose, Aicardi, or Dup15q syndrome was 59.4 convulsive seizures ($n = 46$, IQR: 25–126) and 77.0 total seizures ($n = 50$, IQR: 31–209).

3.3. Monthly seizure frequencies over time

The median monthly convulsive seizure frequency (Fig. 2) for all patients taking CBD decreased from baseline (59.4 [$n = 46$], IQR: 25–126) to week 12 (22.5 [$n = 35$], IQR: 6–80) and week 48 (23.3 [$n = 27$], IQR: 9–74).

For the Aicardi subgroup, there was a $>50\%$ decrease from the median baseline number of seizures (26 [$n = 14$], IQR: 3–67.5) to the median at week 12 (11.5 [$n = 11$], IQR: 1–40), with no difference by week 48 (17 [$n = 7$]) ($\chi^2(2) = 4.56$, $p = 0.102$). The CDKL5 subgroup had a large decrease in seizure frequency from baseline (66.4 [$n = 17$], IQR: 25.9–212.0) to week 12 (35.8 [$n = 11$], IQR: 8.9–141.6) that is statistically significant ($\chi^2(2) = 6.889$, $p = 0.032$). The median frequency by week 48 (25.62 [$n = 10$], IQR: 6.89–75.3) remains consistent from week 12. For the Doose subgroup, there was a $>50\%$ decrease from baseline (60.84 [$n = 7$], IQR: 9–126) and week 12 (16 [$n = 6$], IQR: 1–93), with no difference from week 12 to week 48 (16 [$n = 4$], IQR: 9–56) ($\chi^2(2) = 0.308$, $p = 0.856$). In the Dup15q subgroup, the median number of seizures decreased from baseline (118.5 [$n = 8$], IQR: 18–241) to week 12 (48.8 [$n = 7$], IQR: 5–99), with no change from week 12 to week 48 (53.02 [$n = 6$], IQR: 7–207) ($\chi^2(2) = 3.00$, $p = 0.223$). All pooled syndromes had a combined effect that was largely statistically significant [$n = 46$] ($\chi^2(2) = 19.4$, $p = 0.000061$), with clinical significance in each individual etiology. Post hoc testing revealed a difference in the number of monthly seizures between baseline and week 12 but not between weeks 12 and 48.

3.4. Percent seizure change

The percent change in median monthly convulsive seizure frequency for all patients taking CBD decreased from baseline [$n = 46$] to week 12 (51.4% [$n = 35$], IQR: 9–85%) and week 48 (59.1% [$n = 27$], IQR: 14–86%) (Fig. 3a).

A Friedman comparison indicates that there was a significant difference between the percent changes in monthly convulsive seizure frequency during baseline and week 12, $\chi^2(2) = 22.966$, $p = 0.000010$, with no difference in seizure percent change between weeks 12 and 48 (Table 2).

Table 1a
Demographics—including all participants ($n = 50$, $n = 55$), regardless of primary efficacy criteria.

		Efficacy group ($n = 50$)					Safety group ($n = 55$)
		All	Aicardi	CDKL5	Dup15q	Doose	
Sex	Female	40 (80%)	17 (100%)	18 (100%)	3 (38%)	2 (29%)	44 (80%)
	Male	10 (20%)	0 (100%)	0 (100%)	5 (63%)	5 (71%)	11 (20%)
Age	0–5	16 (32%)	6 (35%)	8 (44%)	1 (13%)	1 (14%)	16 (29%)
	6–11	14 (28%)	2 (12%)	7 (39%)	2 (25%)	3 (43%)	17 (31%)
	12–17	16 (32%)	8 (47%)	1 (6%)	4 (50%)	3 (43%)	16 (29%)
	18+	4 (8%)	1 (6%)	2 (11%)	1 (13%)	0 (0%)	4 (7%)
Number of baseline background ASDs	0	0	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0
	1	5 (10%)	3 (18%)	2 (11%)	0 (0%)	0 (0%)	5 (9%)
	2	16 (32%)	5 (29%)	8 (44%)	0 (0%)	3 (43%)	18 (33%)
	3	19 (38%)	6 (35%)	4 (22%)	7 (88%)	2 (29%)	21 (38%)
	4+	10 (20%)	3 (18%)	4 (22%)	1 (13%)	2 (29%)	10 (18%)
Diagnosis	Aicardi	17 (34%)	–	–	–	–	19 (35%)
	CDKL5	18 (36%)	–	–	–	–	20 (36%)
	Doose	7 (14%)	–	–	–	–	8 (15%)
	Dup15q	8 (16%)	–	–	–	–	8 (15%)

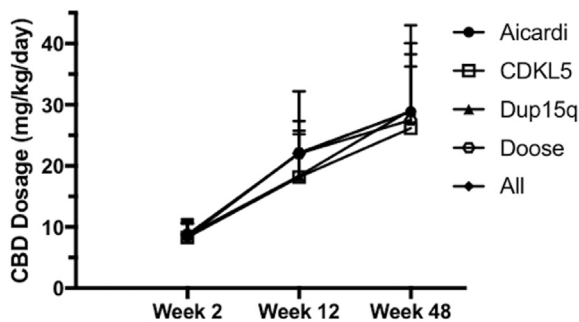


Fig. 1. Dosage of CBD (mg/kg/day) administered to each patient in the Aicardi, CDKL5 deficiency disorder, Dup15q, and Doose subgroups compared with pooled group dosages.

The median percent decrease of convulsive seizures from baseline [$n = 14$] for patients with Aicardi syndrome was 58.3% ($n = 11$, IQR: 40–87%) by week 12, and there was a decrease of 59.2% by week 48 ($n = 7$, IQR: 45–86%). In patients with CDKL5 deficiency disorder, the median convulsive frequency decreased from baseline [$n = 17$] by 40.8% by week 12 ($n = 11$, IQR: 3–65%) and 59.7% by week 48 ($n = 10$, IQR: 5–75%). Patients with Doose syndrome had a median convulsive seizure decrease from baseline [$n = 7$] of 58.6% by week 12 ($n = 6$, IQR: -53 through 96) and 28.8% by week 48 ($n = 4$, IQR: -8 through 92), and those with the Dup15q mutation have a reported median convulsive seizure decrease from baseline [$n = 8$] of 25% by week 12 ($n = 7$, IQR: -10 through 71) and 38.4% by week 48 ($n = 6$, IQR: -13 through 88). The median convulsive seizure frequency for all groups experienced a large net decrease from baseline to week 12, but change was negligible from week 12 to week 48.

3.5. 50% responder rate

The total number of participants across groups with a 50% or greater decrease in convulsive seizure frequency from baseline [$n = 46$] to week 12 was 23 (50%), and by week 48, there were 26 (57%), carrying forward the last observation for those who did not report back for that interval's check-in (Table 2). The percentage of $\geq 50\%$ responders for the Aicardi subgroup was 71% for week 12 and week 48. For patients with CDKL5 deficiency disorder, the percentage of responders at week 12 was 41% and 53% by week 48. The Doose subgroup had a 12-week responder rate of 43% and 57% by week 48. The Dup15q subgroup had a 38% responder rate, which persisted through week 48. The percentage of $\geq 50\%$ responders was variable across the four syndromes but was consistent between the 12- and 48-week time points for each (Fig. 3b).

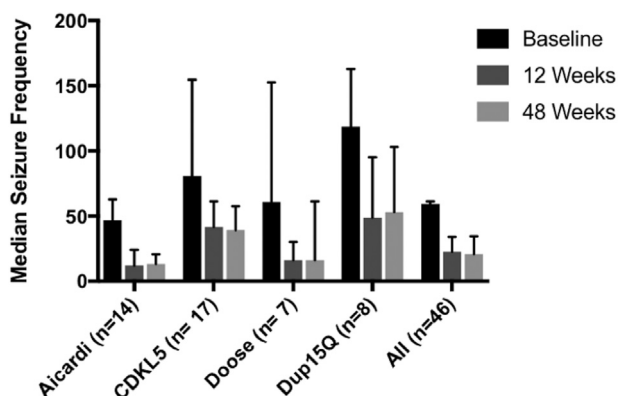


Fig. 2. Median number of convulsive seizures with CBD, efficacy group.

3.6. Background antiseizure drugs

Although patients were strongly encouraged to maintain stable dosages of background antiseizure drugs during the study, some natural fluctuations were observed between time points (Table 1b).

The changes in the most frequently reported background antiseizure drugs were analyzed based on mean background dosage and observed increase or decrease at week 48 compared with baseline (Table 1b). The most common concomitant antiseizure drugs at baseline were clobazam [$n = 25$, 46%] and valproic acid [$n = 20$, 37%]. Across patients, clobazam, valproic acid, levetiracetam, rufinamide, and topiramate each had mean decreases in dosage while lamotrigine dosage remained stable and felbamate had an increased mean dosage. The mean clobazam dosage decreased by 28% from 23.8 mg/day at baseline to 17.1 mg/day by week 48. Mean valproic acid dosage decreased by 29.8% from 757.7 mg/day to 531.8 mg/day, and mean levetiracetam dosage increased by 36% in group from 1393.1 to 1891.7, with the minority (39%) of those taking levetiracetam from baseline to week 48 actually experiencing a net increase in dosage, skewing the group mean. The mean rufinamide dosage decreased 5% from 1252.0 mg/day at baseline to 1185.5 mg/day, and topiramate had a mean 20% decrease in dosage from 125 mg/day to 100 mg/day.

3.7. Adverse events and withdrawal

Of the 55 patients in the safety group, 5 (9%) participants had withdrawn by week 12 of the study, with 2 withdrawals resulting from an adverse event, 1 from withdrawn consent, 1 due to lack of efficacy, and the last being lost to follow-up. Cumulatively, 10 (18%) withdrew by week 48, with 5 between weeks 12 and 48 due to lack of efficacy (4) and adverse event (1). A total of 15 (27%) participants withdrew by week 144 of extended follow-up. Of the withdrawn population, 4 (7%) discontinued participation and cited adverse effects of the CBD as their rationale. For the rest, 9 (16%) patients reported lack of efficacy, 1 (2%) withdrew consent, and 1 (2%) was withdrawn because of lack of follow-up.

In the safety analysis, the most frequently reported adverse events were diarrhea (29%), somnolence (22%), and fatigue (22%). Serious treatment-emergent adverse events included convulsion (9%), status epilepticus (9%), and respiratory infection (5%). There were no deaths (Table 3).

4. Discussion

Our open-label drug trial provides class III evidence for the long-term safety and efficacy of CBD administration in patients with TRE associated with CDKL5 deficiency disorder and Aicardi, Dup15q, and Doose syndromes. Ninety percent of our participants were on two or more antiepileptic drugs (AEDs) at baseline, with seizures still uncontrolled [16–19]. The possibility of refractory seizures leading to status epilepticus or SUDEP necessitates research into alternative or adjuvant therapies, which may relieve this burden by decreasing seizure frequency. While our prior open-label study found similar safety and efficacy of CBD adjuvant therapy in a diverse population of TRE etiologies [7], the current study focused on four of the previous study's most populous syndromes and extended the duration of follow-up from 12 to 48 weeks. Our study adds to the existing data supporting the efficacy of CBD in other epilepsy syndromes and etiologies [12,13].

This study found that adjuvant CBD reduced the frequency of seizures in these four epilepsy etiologies. Our primary efficacy outcome measure was median reduction in convulsive seizures from baseline, which decreased from baseline by 51.4% at week 12 (IQR: 9–85%) and 59.1% at week 48 (IQR: 11–85%), with a nonsignificant change between weeks 12 and 48. This indicates that the improvement in convulsive seizure frequency was stable over time.

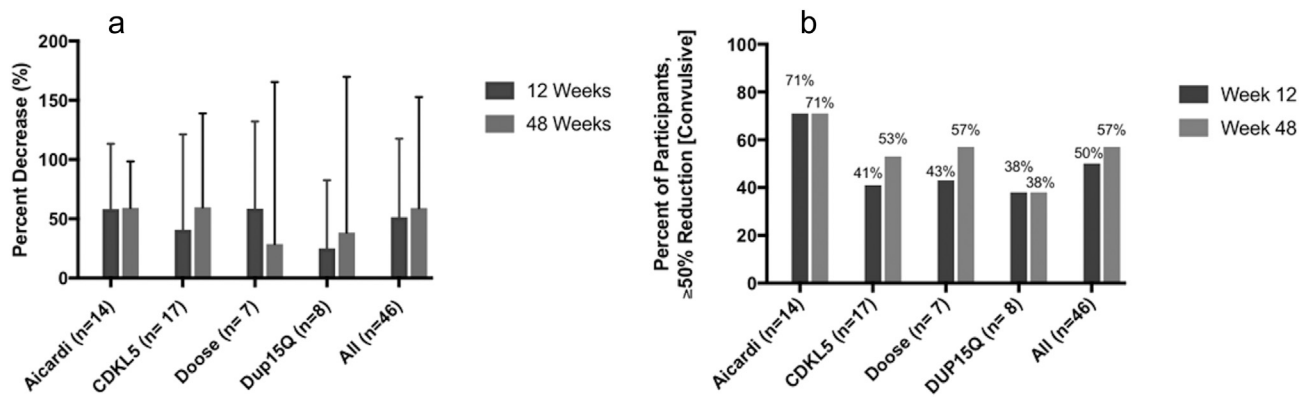


Fig. 3. (a) Median percent change in convulsive seizure frequency with CBD (SD). (b) Responder rate proportion of participants with a reduction in monthly seizure frequency of 50% or more.

The percentage of patients who experienced a 50% or more decrease in convulsive seizures after 12 weeks of follow-up was 50% at 12 weeks and 57% at 48 weeks. Because this was an open-label study in children and young adults and investigators were encouraged to avoid changes in other AEDs or other therapies (e.g., vagus nerve stimulator settings) during the first 12 weeks of CBD therapy, such changes after week 12 could have contributed to ongoing improvement. However, in most cases, other AED dosages were lowered because of side effects or parental requests. We found no evidence for tolerance to the efficacy of CBD. Our observation that tolerance was not a clinical issue is consistent with prior animal studies; one such study in rodents found that although a small increase in tolerance to CBD was witnessed after 3 days of treatment, there was no significant tolerance to the antiseizure properties of CBD after titration and a maintenance period of 22 days with consistent dosage administration [20,21].

A recent pharmacokinetic study found that the only significant interaction of CBD with other AEDs was with clobazam, leading to an increase in the N-desmethyloclobazam metabolite levels [22]. In that study, a similar seizure reduction was reported: 50% mean seizure reduction was seen in the 10 subjects who lowered their clobazam dosage through the study compared to a 55% mean reduction in those who did not [22]. An analysis of 13 patients treated with CBD and clobazam found that CBD is effective in reducing convulsive seizures in treatment-resistant epilepsies, independent of elevated clobazam metabolite levels [23]. Further, side effects of the interaction were alleviated with reduction of clobazam dosage while efficacy remained the same [23]. Our findings support this conclusion: less than half (25/55) of our subjects were on clobazam at baseline and the dosage of clobazam was reduced from an average of 23.8 mg/day at baseline to 17.4 mg/day at week 12 and 17.1 mg/day at week 48 while efficacy remained stable from week 12 to week 48. Other studies found inconsistent changes in valproic acid and other AED levels which were not identified in the prospective pharmacokinetic study although the sample size was limited and additional studies are warranted [24,25].

Side effects of CBD were generally mild and only 7% of patients withdrew because of adverse effects. The most common adverse events were diarrhea, fatigue, and increased somnolence. Status epilepticus was the most severe adverse event observed. This side effect profile is similar to other open-label studies and randomized controlled trials [7,12,13]. Status epilepticus is not rare among children with TRE and was seen in equal percentages of patients in the placebo and CBD groups in the randomized controlled trial in patients with DS [26]. This suggests status epilepticus is likely part of the underlying condition, not an adverse effect of CBD.

There were several limitations of this study, the most important being its open-label design, especially with a highly publicized drug with abundant anecdotal positive evidence. Since parents and some cognitively able patients were aware that they were treated with CBD, the placebo effect may be magnified compared with other treatments. However, the overall median reduction of convulsive seizures in our open label study (58.1%) [7] was similar to the PCRT in DS (39% [20 mg/kg/day] v. 13% in the placebo group) [25], the phase III PCRT for drop seizures in LGS (44% [20 mg/kg/day] v. 22% in placebo) [6], and in another multi-center PCRT in LGS (37% [10 mg/kg/day] v. 42% [20 mg/kg/day] v. 17 in placebo) [27]. The mean placebo response rate in these trials was 17.3%, suggesting that CBD likely exerted antiseizure efficacy independent of the placebo response. As in other studies, we used frequency of convulsive seizures as the primary outcome measure of efficacy since these can be more accurately counted than nonconvulsive seizures. Another limitation is that the number and dosage of concomitant AEDs were not strictly controlled during the trial. Although each participant was instructed to maintain their regimen as consistent as possible, especially during the first 12 weeks, there were cases (e.g., adverse events, seizure clusters) where AED dosages were adjusted.

The median decrease in seizure frequency and adverse event profile during CBD therapy was similar to that reported in larger open-label and PCRTs. Our preliminary study provides support for randomized controlled trials of CBD in other TREs, although it will be challenging

Table 1b

Selected concomitant antiseizure medication mean dosages and dosage change status. Dosage change status represents the predominant category between dosages that decreased, increased, or remained stable during follow-up.

AED (generic)	Baseline		Week 12		Week 48		Dosage change status
	Mean (SD), mg	n	Mean (SD), mg	n	Mean (SD), mg	n	
Clobazam	23.8 (19.9)	25	17.4 (12.3)	17	15.9 (12.4)	13	Decreased (60%)
Valproic acid	757.5 (414.8)	20	632.5 (445.0)	15	531.8 (296.7)	11	Decreased (48%)
Levetiracetam	1393.1 (1039.2)	18	1271.2 (822.2)	13	1891.7 (1185.1)	6	Decreased (39%)
Lamotrigine	199.1 (140.5)	16	200.0 (138.5)	12	278.8 (195.9)	6	Stable (56%)
Rufinamide	1252.0 (685.9)	15	1256.4 (643.0)	11	1185.5 (833.0)	10	Decreased (53%)
Felbamate	1210.3 (805.4)	3	1357.3 (917.8)	3	1420 (1130.1)	3	Increased (67%)
Topiramate	125.0 (66.1)	3	100 (0)	1	100 (0)	1	Decreased (67%)

Table 2
Measures of CBD efficacy as an antiseizure drug.

Parameter	Baseline	Week 12	Week 48	Friedman test
Monthly raw seizure frequency (#, IQR)	59.4 (25–126)	22.5 (6–80)	23.3 (9–74)	$p = 0.000061$ $\chi^2(2) = 19.4$
Decrease from baseline in median seizures (%)	0.00%	50.6%	58.1%	$p = 0.000010$ $\chi^2(2) = 22.9$
Responder rate decrease $\geq 50\%$ (%)	0.0%	50%	57%	–

to generate significant statistical power, given the rarity of these disorders [16–19]. Considering the high morbidity and mortality associated with uncontrolled epilepsy, novel trial design should be considered.

Declaration of interests

ET is a consultant for GW, Zogenix, Upsher Smith, and Aquestive. She receives research funding from GW and is a clinical trial site PI for GW and Zogenix. AP reports research grants from GW, Upsher-Smith, and LivaNova and is a webinar developer for Medscape and American Academy of Neurology. He consults for GW, LivaNova, Supernus, and UCB. JS reports funding from the NIH, NSF, the State of Alabama, Shor Foundation for Epilepsy Research, EFA, Department of Defense, UCB Biosciences, FDA, AES, SAGE Therapeutics Inc., GW Pharmaceuticals, and Eisai, Inc. He serves as a consultant or on an advisory board for SAGE Therapeutics Inc., GW Pharmaceuticals Inc., NeuroPace, Inc., Upsher-Smith Laboratories, Inc., Medical Associates of the State of AL, Serina Therapeutics Inc., LivaNova Inc., and Elite Medical Experts LLC. He is an editorial board member for *Epilepsy & Behavior*, *Journal of Medical Science*, *Epilepsy Currents*, and *Folia Medical Copernicana* and is an associate editor for the *Journal of Epileptology*. AW receives research funding from Zogenix, UCB, and GW Pharmaceuticals and publication royalties from UpToDate and is a consultant for LivaNova. He is also on the Speaker's Bureau for LivaNova and Sunovion. RW has been a clinical trial investigator for Eisai, Sunovion, Biogen, Pfizer, Lundbeck, UCB, SK Life Science, MonoSol, Engage, Upsher-Smith, and GW Pharmaceuticals. He is on an advisory board or consults for UCB, Eisai, Upsher-Smith, Engage, Sunovion, Lundbeck, GW Pharmaceuticals, Alexza, Supernus, Brain Sentinel, and RSC. Recently, he received Speaker Bureau Honoraria for LivaNova, Sunovion, Lundbeck, Eisai, and UCB. DF receives salary support from the Epilepsy Study Consortium. He receives consulting fees from Eisai, GW Pharmaceuticals, Penumbra, Supernus, and UCB.

Table 3
Adverse events observed and withdrawals reported in the safety group ($n = 55$) by week 144 of extended follow-up, with rate of incidence.

Safety analysis	
Total withdrawn	15 (27%)
Lost to follow-up	1 (2%)
Adverse effect	4 (7%)
Lack of efficacy	9 (16%)
Withdrawn consent	1 (2%)
Reported adverse events ^a	
Diarrhea	16 (29%)
Somnolence	12 (22%)
Fatigue	12 (22%)
Decreased appetite	11 (20%)
Convulsion	10 (18%)
Vomiting	10 (18%)
Resp. tract infection	8 (16%)
Weight loss	5 (9%)
Status epilepticus	5 (9%)
Irritability	4 (7%)
Pyrexia	4 (7%)

^a Serious treatment-emergent adverse events included convulsion (5), status epilepticus (5), respiratory infection (3), vomiting (2), diarrhea (1), and weight decrease (1).

He received honorarium for educational materials from Neuropace and receives research funding from UCB and the Epilepsy Foundation as well as royalties from Oxford University Press. OD reports receiving grant support from GW Pharmaceuticals, Novartis, PTC Therapeutics, and Zogenix and holding equity interest in Rettco, Paimomix, Privateer Holdings, Empatica, and Egg Rock.

LL, FF, GC, YP, LS, EMB, RF, and CV report no conflicts of interest or financial disclosures.

Acknowledgment

GW Pharmaceuticals provided study drug, collected and collated the data from all sites, produced standard set of data tables, and sent all results directly to Orrin Devinsky for analysis and interpretation by authors. Open access fees were funded by Greenwich Biosciences. We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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