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Drug–drug interactions with cannabidiol (CBD) appear to have no effect on treatment response in an open-label Expanded Access Program

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ABSTRACT

Objective: We have previously shown that cannabidiol (CBD; Epidiolex®) significantly affects levels of clobazam/N-desmethylclobazam, rufinamide, topiramate, zonisamide, and eslicarbazepine. In the present study, we tested whether the presence of concomitant clobazam affected seizure frequency and severity (treatment response) 12 weeks after initiation of therapy with CBD in patients with treatment-resistant epilepsy (TRE). The secondary questions were whether the presence of any of the other antiepileptic drugs (AEDs) had an effect on seizure frequency or severity at 12, 24, or 48 weeks after therapy initiation.
Methods: One hundred and thirty-two adults and children with TRE receiving CBD were studied prospectively. Participants were separated into two groups — either taking (CBD + clobazam) or not taking concomitant clobazam (CBD − clobazam). In the secondary analyses, participants were divided into groups depending on whether they were taking at least 1/4 of the other AEDs shown to interact with CBD (iAED). Seizure counts and Chalfont Seizure Severity Scale (CSSS) were obtained at baseline, 12, 24, and 48 weeks. Groups were compared at each respective time point in the study using generalized estimating equations (GEE) analyses.
Results: All groups demonstrated statistically significant reductions in seizure frequency and severity from baseline (all $P < 0.05$). When participants on CBD + clobazam were compared with CBD − clobazam, there were no significant differences in seizure frequency and severity reduction between the groups at 12 weeks (both $P > 0.05$). When comparing groups with iAEDs vs. group without iAEDs, independent of coadministration of clobazam, no differences in treatment response were observed (all $P > 0.05$). Longitudinal analyses up to 48 weeks after therapy initiation did not reveal any differences in treatment response between groups.
Conclusion: These analyses suggest that concomitant to CBD, AEDs may not have an effect on reducing seizure frequency and severity in patients with TRE.

1. Introduction

There has long been interest in the use of cannabis and its derivatives in the treatment of epilepsy. However, until recently, the only available information supporting its use existed in the form of anecdotal reports and animal model data [1–7]. Recently, data from Phase III randomized controlled trials have been published which demonstrate that a pharmaceutical formulation of highly purified cannabidiol (CBD) oral solution (Epidiolex®, Greenwich Biosciences) has a statistically significant efficacy compared with placebo for the treatment of seizures associated with Lennox–Gastaut (LGS) and Dravet Syndromes (DS) [8–10]. Additionally, several open-label Expanded Access Programs (EAPs) have reported CBD's efficacy for the management of patients with treatment-resistant epilepsy (TRE) [11–13]. Recently, analyzed data from our open-label CBD program have indicated significant reduction in seizure frequency and seizure severity from pre-CBD baseline, with this improvement remaining stable over 48 weeks [13].

The available data suggest that CBD is generally well-tolerated [14]. However, adverse events and potential drug–drug interactions have been reported including interactions with clobazam [8–11,15,16]. With increasing dose of CBD, levels of both clobazam and its active

Abbreviations: LGS, Lennox–Gastaut Syndrome; DS, Dravet Syndrome; EAP, Expanded Access Program; CBD, cannabidiol; TRE, treatment-resistant epilepsy; AED, antiepileptic drug; iAED, interacting AED; CSSS, Chalfont Seizure Severity Scale; GEE, generalized estimating equations.

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metabolite, N-desmethylclobazam increased in our study [15]. Only levels of N-desmethylclobazam increased in other studies [10,16,17]. The interaction between clobazam and CBD resulted in a higher incidence of sedation that has been explained by CBD's strong inhibition of the cytochrome P450 (CYP) enzyme CYP2C19 [16,18–22]. Further, we have recently shown that CBD may increase the serum levels of rufinamide (mean: 8.8% change from baseline), topiramate (9.7% change), zonisamide (12.2% change), and eslicarbazepine (23.6% change); however, these changes were not associated with any clinical correlates; these increases were within the accepted therapeutic range [15]. The CBD/clobazam interaction has been linked to increased sedation and possible reduction in seizure frequency, but the clinical significance of the other potential drug–drug interactions remains unclear [11,23]. As such, the goals of this study were as follows: 1) to determine if the combination of clobazam and CBD results in a different treatment response and 2) to determine if the presence of any of the other 4 antiepileptic drugs (AEDs) previously shown to increase in level with CBD (interacting AEDs (iAEDs)) has an effect on seizure frequency or severity.

2. Material and methods

The University of Alabama at Birmingham (UAB) CBD program is an ongoing, prospective, open-label, and compassionate-use study investigating safety and efficacy of a highly purified, pharmaceutical formulation of CBD (Epidiolex®, Greenwich Biosciences) in participants with TRE including but not limited to LGS or DS. The study was approved by the UAB Institutional Review Board (IRB), and appropriate Food and Drug Administration (FDA) and Drug Enforcement Agency (DEA) approvals were obtained (clinicaltrials.gov numbers NCT02695537 and NCT02700412); all participants and/or caregivers signed informed consent prior to treatment initiation. Detailed inclusion and exclusion criteria and CONSORT statement were previously published [13]. Treatment-resistant epilepsy was defined as video-electroencephalogram confirmed epilepsy not responding to at least 4 AEDs at adequate doses, including at least one trial of 2 concomitant AEDs. In addition, all AED doses had to be stable for 1 month, and neurostimulator settings/ketogenic diet ratio (if applicable) had to be stable for at least 3 months for the participant to be considered for enrollment. Other inclusion criteria were age >1 year, documentation of a seizure calendar for 3 months prior to enrollment, and Alabama residency. Exclusion criteria included a 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, or felbamate therapy initiation within the 12 months prior to study enrollment. An independent committee approved all participants before enrollment, with review and confirmation of meeting all criteria by study investigators at the time of enrollment.

We evaluated all participants in person every 2 weeks during active CBD dose titration. Longer intervals up to 12 weeks between visits were allowed once CBD dose stabilized. The study design was meant to reflect that of a naturalistic follow-up study [24,25]. All participants received oral formulation of purified CBD in sesame oil. Participants were weighed at every visit, and weight-based CBD dosing was initiated at 5 mg/kg/day and taken twice daily. At each subsequent clinic visit, CBD could be increased in 5 mg/kg/day increments every 2 weeks up to a maximum dose of 50 mg/kg/day. Dose adjustments were made based on seizure response and tolerability. The CBD dose could be decreased over the phone because of seizures or side effects, but dose increases only occurred in person. Additionally, once study procedures began, other AED doses could be adjusted at the discretion of the investigators, most often due to a suspected drug interaction between CBD and other AEDs, but some participants requested to decrease polytherapy with other AEDs during the study.

All data were collected prospectively using standardized forms and questionnaires. Participants were required to maintain detailed seizure

Table 1
Study demographics.

	CBD + iAED	CBD + iAED + clobazam	CBD (no iAED)	CBD + clobazam (no iAED)	Overall	Test statistic
Variables	N = 52	N = 22	N = 37	N = 21	N = 132	
Total seizure frequency	88.2 ± 216.8	229.4 ± 610.7	177.1 ± 510.2	136.9 ± 302.1	144.4 ± 407.9	$\chi^2(3) = 1.45$, P = 0.69[a]
Seizure severity score	86.1.2 ± 70.2	89.5 ± 48.1	70.3 ± 44.1	76.4 ± 46.2	80.7 ± 56.6	$\chi^2(3) = 1.88$, P = 0.6[a]
Age in years	19.8 ± 15.5	16 ± 9.1	24.3 ± 12.2	13.9 ± 5.8	19.5 ± 12.9	$\chi^2(3) = 11.11$, P = 0.01[a]
Age at seizure onset	4.7 ± 7.8	3.2 ± 4.4	5.9 ± 7.2	3.1 ± 3.7	4.5 ± 6.6	$\chi^2(3) = 7.88$, P = 0.05[a]
Gender						$\chi^2(3) = 0.88$, P = 0.83[b]
Female	52% (27)	45% (10)	57% (21)	57% (12)	53% (70)	
Male	48% (25)	55% (12)	43% (16)	43% (9)	47% (62)	
Race						P = 0.37[c]
American-Indian/Alaskan Native	2% (1)	0% (0)	0% (0)	0% (0)	1% (1)	
Asian	4% (2)	5% (1)	0% (0)	0% (0)	2% (3)	
Black/African-American	6% (3)	14% (3)	8% (3)	19% (4)	10% (13)	
Native Hawaiian/Pacific Islander	0% (0)	5% (1)	0% (0)	0% (0)	1% (1)	
White	88% (46)	77% (17)	92% (34)	81% (17)	86% (114)	
Arm						$\chi^2(3) = 6.89$, P = 0.08[b]
Adult	48% (25)	45% (10)	59% (22)	24% (5)	47% (62)	
Pediatric	52% (27)	55% (12)	41% (15)	76% (16)	53% (70)	
History of epilepsy surgery						$\chi^2(3) = 0.74$ P = 0.86[b]
No	71% (37)	68% (15)	65% (24)	62% (13)	67% (89)	
Yes	29% (15)	32% (7)	35% (13)	38% (8)	33% (43)	
Number of AEDs at enrollment	2.8 ± 0.9	3.5 ± 0.7	2.5 ± 0.9	3.1 ± 0.5	2.8 ± 0.9	
Number of iAEDs at enrollment	1.0 ± 0.2	1.2 ± 0.5	–	–		
No. participants iAED wean	7 dose ↓ (13%) 4 dc (8%)	2 dose ↓ (9%) 1 dc (5%)	–	–		
No. participants clobazam wean	–	15 dose ↓ (68%) 1 dc (5%)	–	14 dose ↓ (67%) 2 dc (10%)		

Data are presented as: mean ± SD for continuous variables and column percentages (frequency) for categorical variables. Dc: discontinued; N/A: not applicable.
[a] Test used: Kruskal–Wallis test.
[b] Test used: Pearson chi-square test.
[c] Test used: Fisher's exact test.

Table 2
Means and standard error of means (M ± SEM) of seizure measures across visits and treatment groups.

Visit	N	CBD + iAED	N	CBD + iAED clobazam	N	CBD (no iAED)	N	CBD + clobazam (no iAED)
Seizure severity								
Baseline	52	86.06 ± 9.7	22	89.55 ± 10.3	37	70.31 ± 7.2	21	76.36 ± 10.1
Week 12	51	43.6 ± 6.2	22	47.18 ± 7.5	37	30.76 ± 5	20	35.2 ± 7
Week 24	37	40.49 ± 7	15	43.67 ± 9.8	22	42.41 ± 9.4	14	35.5 ± 8.2
Week 48	28	36.75 ± 7.3	7	36.29 ± 10	14	22.46 ± 5.9	12	42.75 ± 8.1
Seizure frequency								
Baseline	52	88.16 ± 30.1	22	229.36 ± 130.2	37	177.08 ± 83.9	21	136.87 ± 65.9
Week 12	51	41.29 ± 10.7	22	53.27 ± 17.3	37	78.99 ± 29.9	20	31.37 ± 11.2
Week 24	37	31.06 ± 9.7	15	192.98 ± 120.1	22	66.43 ± 34.2	14	25.06 ± 13.3
Week 48	28	23.17 ± 6.8	7	31.52 ± 22.1	14	110.13 ± 63.1	12	36.62 ± 22.7

calendars that were reviewed at each study visit. "Seizure frequency" was calculated as a number of all seizures per 14 days averaged over the preceding 12 weeks; seizure frequency after CBD initiation was calculated between visits and provided as an average over 14 days. While data were collected on all seizure types, in many cases, there was no clear demarcation between seizure types and/or participants, caregivers, and providers labeled seizures differently. As a result, analyses based on seizure type would likely be less reliable than analyses based on a total seizure count; similar analyses based on all seizure types were presented in the reports of the randomized clinical trials [8,9,17]. Seizure severity was measured with the Chalfont Seizure Severity Scale (CSSS), which 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 in 10 points or more on CSSS is considered clinically significant [26]. Similarly, to seizure frequency, CSSS was reported in this study as the total CSSS for all seizure types. Serum AED levels were checked at every study visit (this did not include serum CBD levels).

This analysis encompasses the accrual during the first 2 years of the study; 139 participants received at least one study visit of this cutoff date, and 132 had at least 1 follow-up visit. Our aim was to investigate whether changes in seizure frequency and severity in our CBD program were affected by the presence of iAEDs [15,16]. The analysis was carried out in three parts. First, we compared all participants taking clobazam and CBD (CBD + clobazam) vs. participants not taking clobazam (CBD − clobazam) and determined if there were differences between these two groups in regard to treatment response at 12 weeks. Second, we compared all participants taking at least 1 of 4 iAEDs (rufinamide, eslicarbazepine, zonisamide, topiramate; CBD + iAEDs) versus participants not on iAEDs (CBD − iAED) and determine if there were differences between these 2 groups in treatment response at 12 weeks. Finally, we made these same comparisons longitudinally to determine if there are differences in seizure frequency and severity with concomitant clobazam and/or any of the 4 iAEDs at 24 or 48 weeks. The window around the assessment times was allowed given the variable length of time between visits depending on CBD dose changes as described above (2 at 12, 4 at 24, and 6 at 48 weeks follow-up). When multiple visits fell within the designated range, the encounter closest to the 12-, 24-, or 48-week visit was used. The numbers of participants at each respective follow-up visit were lower than the initial numbers because 1) a given participant had not been enrolled in the study for this amount of time by the time of the cutoff date or 2) a participant dropped out of the study because of lack of efficacy or adverse events. Clobazam was separated from the other iAEDs because of previously published evidence that treatment response may be enhanced by the presence of concomitant clobazam [11,23]. These analyses were performed with the negative binomial regression model using generalized estimating equations (GEE) analysis. The GEE analysis was chosen as it allowed us to use all of the data despite censoring due to enrollment date.

3. Results

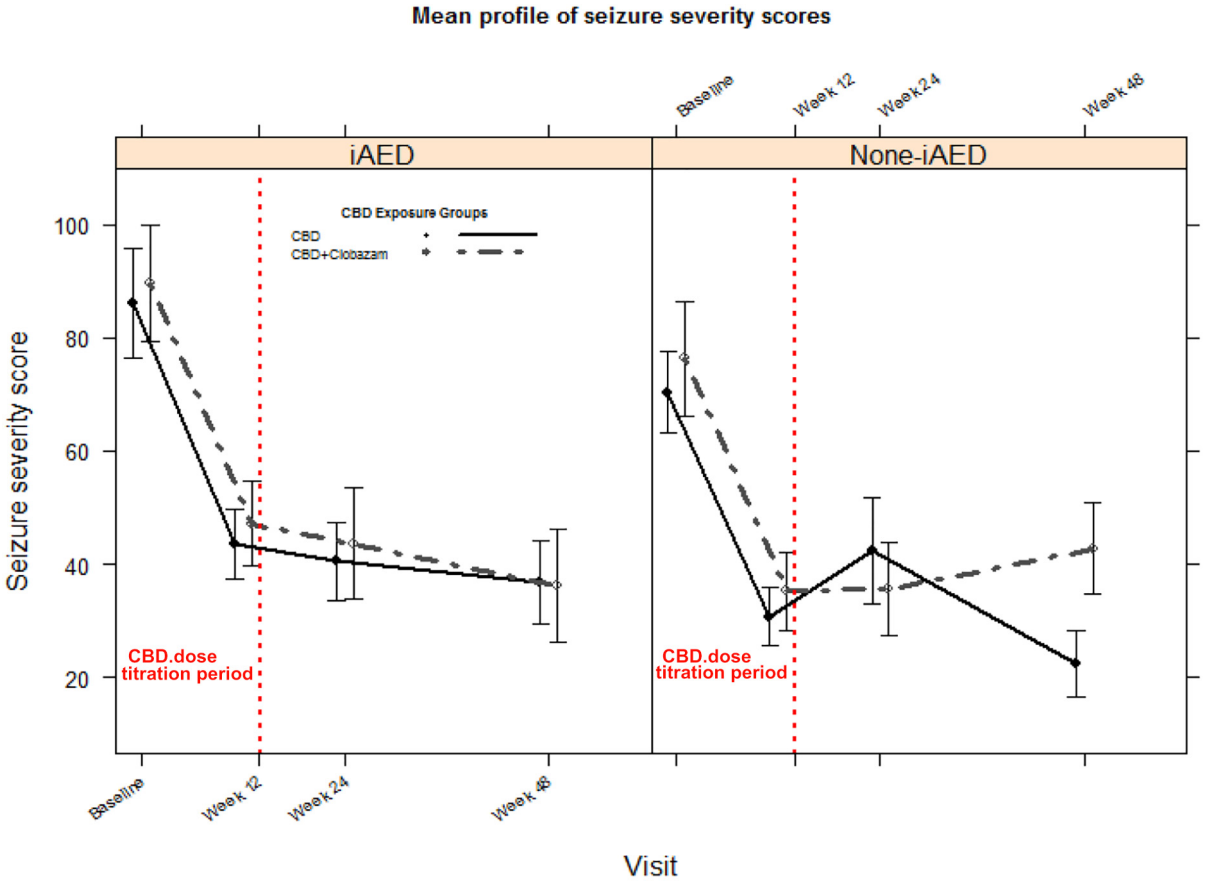
Demographics for the four groups in this analysis are presented in Table 1. All variables (including seizure frequency and severity at enrollment) were similar across these four groups, with the exception of age distribution at baseline in some of the groups (see Table 1). A participant was deemed eligible for this analysis if he or she had enrollment data and at least one qualifying follow-up visit. Of the 139 participants enrolled during the 2-year period until the cutoff date, 132 (70 adults, 62 children) with at least one follow-up visit at 12 weeks were included in these analyses. Out of the 132 participants, 43 were taking clobazam, 74 were taking at least one of the other iAEDs +/− clobazam, while the rest were taking no iAEDs. Among the 74 subjects taking iAEDs, 22 were taking CBD + clobazam. While the data are presented in the 4-group format, all participants taking clobazam (with or without the presence of iAED) were analyzed separately for seizure frequency and severity changes. We detail the frequency of iAED and/or clobazam dose adjustments or discontinuation in Table 1.

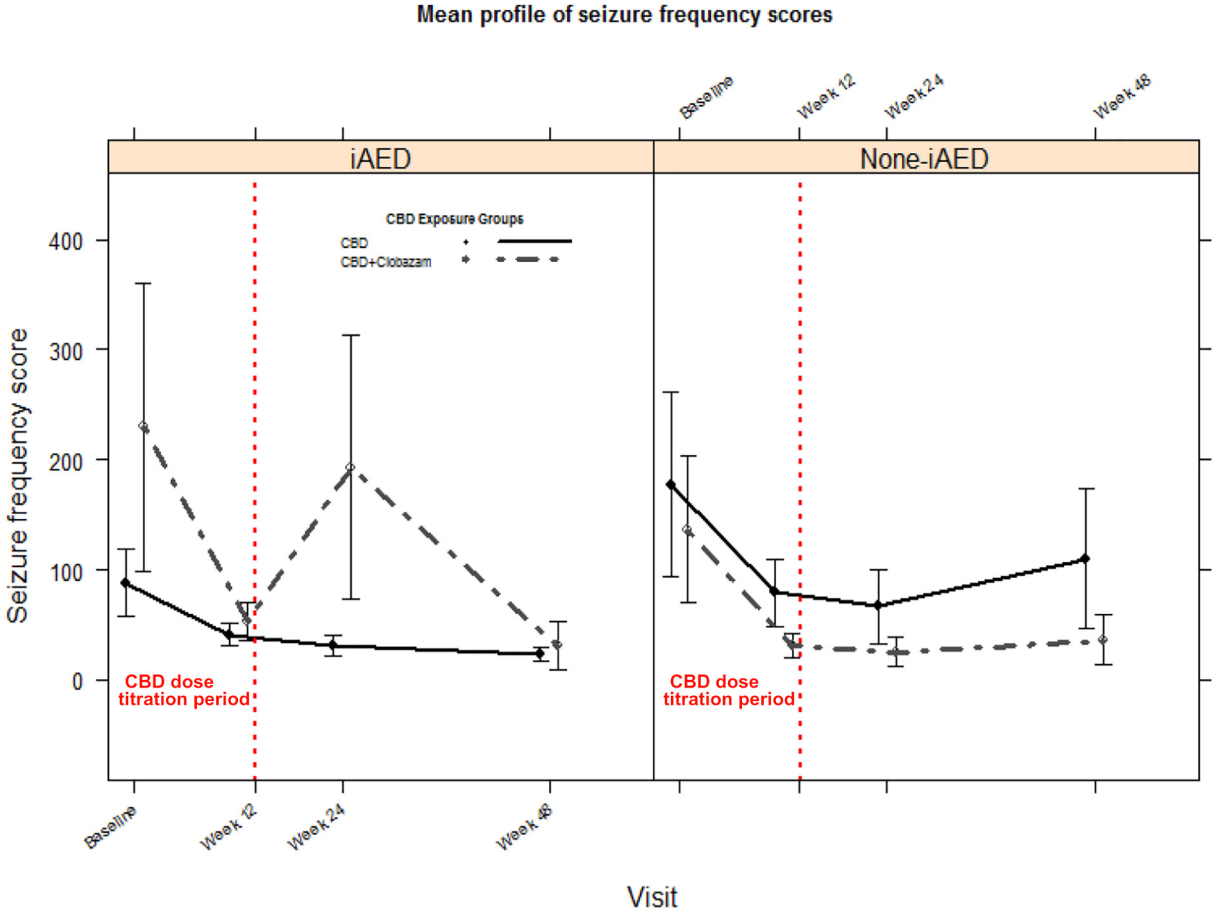
Participants in all groups had significant treatment response to CBD compared with their baseline seizure frequency and severity (Tables 2 and 3). Our primary analysis investigating whether the presence of iAEDs affected treatment response to CBD or not at 12-week follow-up revealed that seizure frequency and severity reduction were not dependent on the presence of clobazam or any of the other 4 iAEDs. Groups were not further compared at each respective time point since the overall interaction effects in both models were not significant. The final model that excluded nonsignificant 2- and 3-way interactions revealed no differences in reduction in seizure frequency and severity

Table 3
GEE estimates of changes in seizure severity and frequency over the 48-week period of study.

Variables	Seizure severity model		Seizure frequency model	
	Effect (95%CI)	P-value	Effect (95%CI)	P-value
CBD				
CBD vs CBD + clobazam (ref.)	−0.09 (−0.3, 0.1)	0.4395	−0.3 (−1.3, 0.7)	0.5505
AEDs				
iAED vs non-iAED (ref.)	0.2 (0, 0.4)	0.1106	−0.33 (−1.3, 0.6)	0.4946
Visit				
Week 12 vs Baseline (ref.)	−0.73 (−0.9, −0.6)	<0.0001	−0.97 (−1.3, −0.6)	<0.0001
Week 24 vs Baseline (ref.)	−0.68 (−0.9, −0.5)	<0.0001	−0.76 (−1.2, −0.3)	0.0003
Week 48 vs Baseline (ref.)	−0.85 (−1.1, −0.6)	<0.0001	−1.14 (−1.6, −0.6)	<0.0001

Overall visit effect in final model: Seizure severity model: $\chi^2(3) = 53$, $P < 0.0001$; Seizure freq. model: $\chi^2(3) = 10$, $P = 0.0145$ All 2- and 3-way interactions terms were excluded from final output model because of nonsignificance:
Seizure severity model: CBD * AED * Visit Test: $\chi^2(3) = 3.4$, $P = 0.34$.
Seizure frequency model: CBD * AED * Visit Test: $\chi^2(3) = 4.3$, $P = 0.23$.


Mean profile of seizure severity scores
Baseline
Week 12
Week 24
Week 48
iAED
None-iAED
CBD Exposure Groups
CBD
CBD+Clobazam
Seizure severity score
100
80
60
40
20
CBD.dose titration period
CBD.dose titration period
Baseline
Week 12
Week 24
Week 48
Visit


Mean profile of seizure frequency scores
Baseline
Week 12
Week 24
Week 48
iAED
None-iAED
CBD Exposure Groups
CBD
CBD+Clobazam
Seizure frequency score
400
300
200
100
0
CBD dose titration period
CBD dose titration period
Baseline
Week 12
Week 24
Week 48
Visit

between CBD + clobazam/CBD − clobazam groups or between CBD + iAED/CBD − iAED groups (Table 3 and Fig. 1). Treatment response overall was sustained over the full 48-week study period in all groups ($P < 0.015$; Tables 2 and 3), and evidence from the GEE analysis did not support longitudinal differences in treatment response between the CBD groups.

4. Discussion

This study investigated whether iAEDs had an effect on treatment response to CBD in patients with refractory epilepsy. Overall, our study cohort appears to be well suited for this analysis as the response to CBD observed in our participants is in line with the response observed in the randomized controlled trials [14]. However, the focus of the current analysis was on whether the coadministration of clobazam and/or iAEDs (topiramate, zonisamide, rufinamide, or eslicarbazepine) resulted in different treatment response. Our data suggest that there may not be a differential effect of various combinations on improving seizure frequency or severity with CBD (lack of pharmacodynamics effect).

Our findings may be clinically significant as they suggest that the efficacy of CBD for epilepsy may not be dependent on the presence of other concomitant AEDs, particularly clobazam. These results are in contrast to two other observational studies that showed increased responder rates in participants taking concomitant clobazam [11,23]. In one open-label observational study of patients with treatment-resistant epilepsy, 51% of participants taking clobazam had a ≥50% reduction in motor seizure frequency at 12 weeks, compared with 27% of the participants not taking clobazam. In the study's post hoc analysis, the presence of concomitant clobazam independently predicted reduction of ≥50% of motor seizures [11]. In another open-label study investigating a subset of participants enrolled with tuberous sclerosis complex, the 50% responder rate at 3 months was 58.3% in the 12 participants taking clobazam vs. 33.3% in the 6 participants not taking clobazam [23]. Our study's sample size is somewhat comparable with the first open-label study; however, difference in results may be explained by both of these analyses being exploratory and study design not powered to answer this question specifically.

There were other limitations of our analyses. First, the open-label and naturalistic follow-up study design does not allow for controlled conditions. Even though AED doses had to remain stable for 1 month prior to study enrollment, the doses were allowed to change once study procedures begun (Table 1). We were not able to account for specific doses of the other AEDs in our analyses as there was no specific pattern to the adjustments. While other AED doses were not changed in a majority of participants, given the known interaction between CBD and clobazam, the clobazam dose was frequently decreased because of increased serum clobazam and N-desmethylclobazam levels and resulting sedation (see Table 1 for specific numbers of iAEDs and reductions/discontinuation of clobazam in our study participants). This approach may be masking a possible effect of increasing levels of N-desmethylclobazam on treatment response. Although we overall present a large dataset to address this issue, a limitation of our analysis is a relatively small sample size for most of the groups, particularly at the 24- and 48-week follow-up visits. These low sample sizes resulted in relatively low power to detect subtle differences. Thus, whether our findings are due to the open-label flexible treatment design or if no actual differences exist may be confounded by study design. A similar analysis needs to be performed under controlled conditions, particularly in the setting of no or minimal clobazam dose adjustment. Finally, our study did not monitor CBD serum levels during CBD titration; thus, it is unclear if there was any effect of other AEDs on CBD levels. As we have shown previously, there is a relationship between CBD dose, CBD level, and seizure response [27].

In summary, this study suggests that highly purified CBD oral solution is effective in reducing seizure frequency and severity from baseline in adults and children with TRE. Further, it appears that these reductions may not be dependent on the pharmacokinetic drug–drug interactions between CBD and clobazam, topiramate, zonisamide, rufinamide, and eslicarbazepine. However, our results should be interpreted with caution given several confounders including decreasing sample sizes in the latter follow-up visits and thus low power and our naturalistic, open-label study design which allowed dose changes of other AEDs once a participant was enrolled in the study.

Declaration of Competing Interest

Tyler Gaston — Salary support from the State of Alabama ("Carly's Law"), Consulting Fee from Greenwich Biosciences, Inc.

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Fig. 1. Mean profile plots showing changes in seizure frequency and severity over the 48-week period in participants taking at least 1 of 4 other iAEDs and participants not taking an iAED. Participants taking concomitant clobazam are plotted separately.

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