FULL-LENGTH ORIGINAL RESEARCH

Interactions between cannabidiol and commonly used antiepileptic drugs

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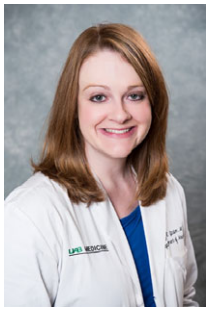

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Summary

Objective: To identify potential pharmacokinetic interactions between the pharmaceutical formulation of cannabidiol (CBD; Epidiolex) and the commonly used antiepileptic drugs (AEDs) through an open-label safety study. Serum levels were monitored to identify interactions between CBD and AEDs.

Methods: In 39 adults and 42 children, CBD dose was started at 5 mg/kg/day and increased every 2 weeks by 5 mg/kg/day up to a maximum of 50 mg/kg/day. Serum AED levels were obtained at baseline prior to CBD initiation and at most study visits. AED doses were adjusted if it was determined that a clinical symptom or laboratory result was related to a potential interaction. The Mixed Procedure was used to determine if there was a significant change in the serum level of each of the 19 AEDs with increasing CBD dose. AEDs with interactions seen in initial analysis were plotted for mean change in serum level over time. Subanalyses were performed to determine if the frequency of sedation in participants was related to the mean serum *N*-desmethylclobazam level, and if aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were different in participants taking concomitant valproate.

Results: Increases in topiramate, rufinamide, and *N*-desmethylclobazam and decrease in clobazam (all $p < 0.01$) serum levels were seen with increasing CBD dose. Increases in serum levels of zonisamide ($p = 0.02$) and eslicarbazepine ($p = 0.04$) with increasing CBD dose were seen in adults. Except for clobazam and desmethylclobazam, all noted mean level changes were within the accepted therapeutic range. Sedation was more frequent with higher *N*-desmethylclobazam levels in adults ($p = 0.02$), and AST/ALT levels were significantly higher in participants taking concomitant valproate ($p < 0.01$).

Significance: Significantly changed serum levels of clobazam, rufinamide, topiramate, zonisamide, and eslicarbazepine were seen. Abnormal liver function test results were noted in participants taking concomitant valproate. This study emphasizes the importance of monitoring serum AED levels and LFTs during treatment with CBD.

KEY WORDS: Cannabidiol, Interactions, AEDs, Clobazam, Valproate.

For millennia, there has been great interest in the use of cannabis and its derivatives in the treatment of various medical and neurologic problems, including epilepsy.[1,2] Cannabidiol (CBD), a phytocannabinoid compound derived from the cannabis plant, is of particular interest as a potential anticonvulsant due to the reported lack of psychoactive effects compared to those seen in tetrahydrocannabinol (THC). CBD has long been known to be effective in animal models of epilepsy.[3–7] However, until recently, few data were available regarding its safety and efficacy in humans.

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Key Points

- Serum levels of topiramate, rufinamide, and *N*-desmethylclobazam increased in children and adults with increasing CBD dose
- Serum levels of zonisamide and eslicarbazepine increased in adults with increasing CBD dose
- Adult participants reported sedation more frequently with higher *N*-desmethylclobazam levels
- AST and ALT levels were higher in participants taking concomitant valproate with CBD

Recent placebo-controlled studies indicate that CBD may be effective for the treatment of difficult-to-control epilepsies including Dravet and Lennox-Gastaut syndromes.[8–10] These experimental data are supported by observational data from class IV open-label compassionate-use CBD state-sponsored expanded-access programs, such as the one in Alabama recognized under the name "Carly's Law."[11–13]

CBD modulates several cytochrome P450 (CYP) enzymes, which are of potential interest in investigating interactions with other medications. It is a potent inhibitor of CYP2C19, CYP2D6, and CYP2C9 and a potential inhibitor of the CYP3 family.[14–20] Based on what is known about CBD's metabolism and the metabolism of other antiepileptic drugs (AEDs), one could speculate that there could be many interactions given the pervasive involvement of these CYP enzymes in the metabolism of AEDs.[21,22] To date, there are few data on CBD's interactions with other AEDs. An animal study using maximal electric shock and audiogenic seizure models showed that CBD potentiated the anticonvulsant effects of phenytoin by twofold, and modestly potentiated the effect of phenobarbital; CBD also reduced the anticonvulsant properties of chlordiazepoxide, clonazepam, and ethosuximide.[23] These results were thought to be due to CBD's actions on the CYP system, although these specific actions were not known at the time. A recently published article revealed a clear drug–drug interaction between CBD and clobazam in a group of 13 pediatric patients. Clobazam and, to a greater extent, *N*-desmethylclobazam (the active metabolite of clobazam) levels increased in response to increasing doses of CBD.[24] Interactions with other AEDs have not been investigated to date.

The University of Alabama at Birmingham (UAB) CBD open-label compassionate-use study is investigating CBD as a potential add-on therapy for the treatment of treatment-resistant epilepsy in children and adults. All the enrolled patients were taking multiple concomitant AEDs. As part of the study, frequent monitoring of serum AED levels was performed to identify potential interactions, changes in drug levels, and possible clinically significant relationships between drug level changes and any observed adverse events. Given what is known about CBD's mechanism of action and metabolism, it was suspected that other AEDs with metabolism hinging on similar enzymes would be affected. The purpose of this study was to identify which AEDs potentially interact with CBD based on serum drug level changes, and in turn, if these potential interactions were clinically meaningful. Based on recently published studies and the known CBD metabolic pathways, we hypothesized that as the dose of CBD increased, the levels of clobazam and *N*-desmethylclobazam would increase.[20,24,25] This potential interaction was hypothesized to contribute to a significant increase in reported excessive sedation in participants taking CBD. Based on observations during the study, we hypothesized that participants taking concomitant valproate with CBD would have a higher incidence of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) abnormalities compared to participants not taking valproate. We also hypothesized that there are interactions with other AEDs given CBD's known action on key CYP enzymes, and thus we examined data on all AEDs used in the study by the enrolled participants.

Methods

The UAB CBD program conducts a prospective compassionate-use open-label study in patients with treatment-resistant epilepsy. "Treatment resistant" was defined as failing to respond to a total of four or more AEDs at adequate dose, including at least one trial of two concomitant AEDs. Other inclusion criteria include age >1 year, stable neurostimulator settings, and ketogenic diet ratio for ≥3 months if applicable, documentation of a detailed seizure diary 3 months prior to enrollment, and current Alabama residency. Exclusion criteria include history of substance abuse or addiction, use of medical marijuana or CBD-based product within the last 30 days, history of allergies to CBD or marijuana products or to sesame, felbamate therapy initiation within the last 12 months, AST or ALT elevation ≥5 times upper limit of normal, hemoglobin <10, hematocrit <30, or white blood cell count <2,000, among others (all inclusion and exclusion criteria are available at www.uab.edu/cbd). Of importance for these analyses is that all participants must have been taking a stable dose of all AEDs for at least 1 month before they could be considered for enrollment. In addition, baseline plasma levels of all AEDs were obtained prior to enrollment.

All participants were seen and evaluated in a devoted research clinic that was held weekly for both adult and pediatric arms of the study. Each potential participant in the study must have a packet submitted on their behalf by their primary neurologist, and all study packets were reviewed by a study approval committee before a participant was enrolled, with second verification by the study principal investigators. At the time of the enrollment visit, all participants and/or their legal representatives signed the consent form that was approved by the University of Alabama at Birmingham Institutional Review Board. The study is U.S. Food and Drug Administration (FDA)

approved and registered with www.clinicaltrials.gov under the numbers NCT02695537 (pediatric arm) and NCT02700412 (adult arm).

Upon approval for enrollment, participants were seen in the clinic every 2 weeks during active titration of the CBD dose, with less frequent appointments when doses were not adjusted. All participants received the active study drug. Epidiolex is formulated in sesame oil and administered orally.[26] Participants were weighed at every clinic visit. All participants were started on a dose of 5 mg/kg/day split between a.m. and p.m.; participants were instructed to take the CBD at the same time they administer their other AEDs dosed twice daily (although this was not strictly monitored). At each follow-up clinic visit, the dose could be titrated in 5 mg/kg/day increments to a maximum dose of 50 mg/kg/day. Dose adjustments were based on participants' response to treatment and tolerability. The dose could be decreased over the phone between clinic visits if there are reports of worsening seizures or side effects, but dose increases were made in person only. Study visit interval was extended once a participant had reached a stable dose of CBD for greater than 2 visits.

At each clinic visit, participants received a full physical examination including neurologic examination and laboratory testing, and their seizure diary and side effect profiles were reviewed. Laboratory testing included complete blood count with differential, comprehensive metabolic panel, and serum AED levels, which were obtained at almost all clinic visits; blood for labs was drawn between 11:00 a.m. and 3:00 p.m. Not all blood samples were collected at trough; therefore, some blood levels were not trough concentrations. Investigators had the authority to adjust the dose of other AEDs if their clinical impression was that a reported adverse event is related to the AED itself or a suspected interaction between that AED and CBD—this follows the design of a naturalistic follow-up study.[27,28] In some cases, particularly with valproate and clobazam, AEDs were weaned and ultimately discontinued due to reports of certain adverse events, notably sedation and elevation of liver function test results.

This analysis encompasses the first year of data collection. AED levels from 39 adults and 42 children were available for analyses. Prior to enrollment, baseline drug levels were obtained by the referring physician and analyzed locally or by designated reference laboratories. Blood samples for drug levels during the study were all drawn in the UAB Kirklin Clinic or Children's Hospital of Alabama (COA) laboratory and were analyzed either by the UAB or COA laboratory or reference laboratories, as necessary; if reference laboratories were utilized, the same service was used each time a specific test was obtained. For example, testing of clobazam and desmethylclobazam was always conducted by Mayo Clinic. All testing was performed in Clinical Laboratory Improvement Amendments (CLIA)-certified laboratories (www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/).

In addition to the baseline AED levels obtained before study enrollment, each visit in which AED levels were obtained was considered a data point. Each data point was associated with a corresponding CBD dose. Using a mixed linear model (the Mixed Procedure), the data points associated with each AED were analyzed to investigate if the plasma levels of each AED changed significantly with increasing CBD dose. In this analysis, absolute changes in serum levels were investigated only; there was no threshold set for each drug to determine clinical significance. To further quantify the degree of change in AED levels on CBD and to account for the noise in the data related to the naturalistic study design, the baseline and first two recorded AED levels were plotted by the mean change in level between measurements (CBD dose was not accounted for in this analysis). Separate subanalyses were performed to determine if there was a significant increase in reported sedation in participants who were taking concomitant clobazam, and if there was a significant increase in AST and ALT levels in participants who were taking concomitant valproate compared to baseline liver function test values obtained at study entry. These adverse events did not occur frequently with the other AEDs, and thus due to lack of clinical suspicion, these subanalyses were performed only on participants taking clobazam and valproate.

Results

Demographic and clinical characteristics of the participants are included in Table 1. Data were analyzed within individual adult and pediatric arms and combined. In some cases, data for a specific AED could be analyzed only within one arm due to insufficient data points for analysis in the

Table 1. Study demographics

	Pediatric arm	Adult arm
N	42	39
Age	10.4 ± 5.3 years (range 2–19)	29.1 ± 11.3 years (range 19–62)
Gender	20 Female 22 Male	20 Female 19 Male
Age at seizure onset	2.4 ± 3 years	7.2 ± 8.7 years
Duration of epilepsy at enrollment	7.9 ± 4.9 years	22.2 ± 8.6 years
Number of AEDs taking at enrollment	3.0 ± 1.0	3.2 ± 0.9
Number of AEDs previously tried	8.8 ± 3.1	10.4 ± 3.9
Surgical procedures	VNS: 12 Resection only: 2 VNS + resection/CC: 2	VNS: 13 Resection: 4 VNS + resection/CC: 5
Types of seizures	Partial only: 8 Generalized only: 28 Both: 6	Partial only: 26 Generalized only: 8 Both: 5

Values are means ± standard deviations. VNS, vagus nerve stimulator; CC, corpus callosotomy.

other arm (carbamazepine, eslicarbazepine, ezogabine, and pregabalin in children, and ethosuximide and vigabatrin in adults). However, in several cases there were >100 data points analyzed for each AED (Table 1). Analysis via the Mixed Procedure allowed us to control for nonuniform changes in both CBD dose and AED doses as allowed in the naturalistic study design. Linear increases in serum levels of topiramate ($p < 0.001$), rufinamide ($p = 0.004$), and *N*-desmethylclobazam ($p < 0.001$, active metabolite of clobazam), and linear decreases in levels of clobazam ($p < 0.001$) with increasing CBD dose were seen in combined pediatric and adult arms (the decreases in clobazam level were concurrent to the decreases in dose as directed by the presence of the adverse effect—sedation). In addition, a significant increase in serum levels of zonisamide ($p = 0.017$) and eslicarbazepine ($p = 0.039$) with increasing CBD dose was seen in the adult arm only. Of note, there were no pediatric participants enrolled in the study who were taking eslicarbazepine at the time of this analysis, and thus an interaction between CBD and eslicarbazepine could not be performed in the pediatric arm. There were no significant changes in drug levels with CBD dose titration in the other AEDs analyzed (valproate, levetiracetam, phenobarbital, clonazepam, phenytoin, carbamazepine, lamotrigine, oxcarbazepine, ethosuximide, vigabatrin, ezogabine, pregabalin, perampanel, and lacosamide). Table 2 shows the results of the analyses for each of the AEDs.

To quantify the degree of change of the AED levels, while accounting for the noise in the data related to the naturalistic study design (namely the investigators' ability to adjust AED and CBD doses during the study), plots were generated to show the mean change in the AED level from the baseline level (off CBD) to the first and second AED levels obtained while the patients was receiving CBD in the AEDs identified to have statistically significant interaction (Table 2). Two separate plots for the same AED were generated if the dose of the AED in question was changed between the measurements (due to elevated levels or possible side effects; this was always an AED dose decrease). This analysis was independent of the CBD dose. There were statistically significant increases in clobazam, N-desmethylclobazam, and eslicarbazepine levels. However, changes in topiramate, zonisamide, and rufinamide levels were not found to be significant in combined arms and within individual pediatric and adult arms when conducted only for the baseline and first two serum AED level measurements. These data are presented in Table 3.

A linear regression model analysis was used to determine if there was a relationship between mean *N*-desmethylclobazam levels and the total frequency of sedation for each participant. A total of 6 of 12 adults and 8 of 15 children taking clobazam during the study complained of sedation at least once during the study, which resulted in a clobazam dose decrease in all instances (but not discontinuation). There was a significant effect of mean level of *N*-desmethylclobazam on the total frequency of sedation ($p = 0.019$), conditioning on the average dose of CBD for adult arm. However, the results were not significant with identical analyses in all study patients and within the pediatric arm.

Table 2. AED level analysis

AED	Adults	Children	Total	Interaction?	p-Value
Clobazam/desmethylclobazam[a]	12 (137)	15 (66)	27 (203)	Y	<0.001
Valproate	8 (82)	14 (69)	22 (151)	N	NS
Levetiracetam	9 (92)	11 (54)	20 (146)	N	NS
Phenobarbital	3 (21)	2 (9)	5 (30)	N	NS
Clonazepam	11 (46)	14 (10)	25 (56)	N	NS
Phenytoin	2 (19)	1 (7)	3 (26)	N	NS
Carbamazepine	4 (29)	0	4 (29)	N	NS
Lamotrigine	16 (139)	14 (68)	30 (207)	N	NS
Oxcarbazepine	6 (60)	6 (19)	12 (79)	N	NS
Ethosuximide	0	5 (22)	5 (22)	N	NS
Topiramate[a]	11 (109)	9 (35)	20 (144)	Y	<0.001
Vigabatrin	0	3 (11)	3 (11)	N	NS
Zonisamide[a]	7 (70)	7 (40)	14 (110)	Y (adult only)	0.017
Eslicarbazepine[a]	4 (25)	0	4 (25)	Y	0.039
Ezogabine	4 (20)	0	4 (20)	N	NS
Pregabalin	2 (15)	0	2 (15)	N	NS
Perampanel	3 (7)	5 (33)	8 (40)	N	NS
Rufinamide[a]	6 (62)	10 (48)	16 (110)	Y	0.004
Lacosamide	12 (103)	8 (37)	20 (140)	N	NS

AED levels were analyzed via Mixed Procedure to determine if there was a significant change in a drug level with increasing dosages of CBD. Under the Adult and Pediatric Arm columns, the first number represents the number of participants in each arm analyzed, while the number in parentheses represents the number of observations or data points used in the analysis. There were significant increases in levels of *N*-desmethylclobazam, topiramate, zonisamide, eslicarbazepine, and rufinamide and decrease in levels of clobazam seen in the analysis, and are noted with[a].

Table 3. Quantification of AED level changes

AED level	N	Mean baseline level	Mean first "on CBD" level	Mean second "on CBD" level	Normal AED level range (trough)
Clobazam[a]	27	264.7 ± 136.3	331.1 ± 143.2 (dose unchanged) 430.3 ± 327.6 (dose decreased)	310.9 ± 104.2 (dose unchanged) 285.0 ± 176.0 (dose decreased)	30–300 ng/ml
N-desmethylclobazam[a]	26	2,207.5 ± 1,854.0	3,727.7 ± 1,549.3 (dose unchanged) 6,226.8 ± 4,006.9 (dose decreased)	3,696.8 ± 1,027.1 (dose unchanged) 4,843.8 ± 2,982.6 (dose decreased)	300–3,000 ng/ml
Eslicarbazepine[a]	4	14.4 ± 7.4	16.8 ± 7.9	17.8 ± 9.1	2–28 μg/ml
Topiramate	20	10.3 ± 5.9	10.8 ± 7.0	11.3 ± 8.3	4.5–20 μg/ml
Zonisamide	14	17.2 ± 12.2	19.3 ± 13.0	17.2 ± 9.3 (dose unchanged) 42.0 (dose decreased in 1 adult)	10–40 μg/ml
Rufinamide	14	24.8 ± 12.8	25.6 ± 13.6	27.0 ± 14.7 (dose unchanged) 12.2 (dose decreased in one child)	5–55 μg/ml

AED levels that were identified to have statistically significant changes in the presence of CBD were further analyzed to determine the degree in change of AED level over time from pre-CBD baseline to the first two blood levels after the initiation of CBD. Due to the naturalistic study design, CBD dose was not accounted for in this analysis. AEDs marked with an asterisk (clobazam $p = 0.030$, desmethylclobazam $p < 0.001$, and eslicarbazepine $p = 0.008$, marked with[a]) showed a statistically significant increase in mean level with the presence of CBD between the baseline and presented in the table time point. Discrepancies in number of participants between Table 2 and here are due to lack of baseline *N*-desmethylclobazam in one participant, and lack of follow-up rufinamide levels in two participants due to quick withdrawal from the study.

Subanalysis of liver function tests was performed with *t*-test and the test of fixed effects. Preliminary analyses in all patients via *t*-test revealed that AST and ALT levels were significantly higher in participants taking concomitant CBD and valproate compared to participants not taking valproate. Valproate and CBD were discontinued in 4 of 14 children due to elevated liver function test results of greater than three times the upper limit of normal, and valproate only was discontinued in one of 8 adults due to liver function test levels approximately two times the upper limit of normal. In all cases, levels normalized quickly after the aforementioned medication changes. Mean ALT level in all participants taking concomitant valproate was 35.3 U/L (normal range 7–52), versus 23.7 U/L in the participants not taking valproate ($p = 0.026$). Mean AST in the participants taking concomitant valproate was 37.1 U/L (normal range 12–39), versus 23.97 U/L in the participants not taking valproate ($p = 0.003$). Furthermore, via the test of mixed effects (mixed model analysis), the effect of valproate on participants' AST and ALT levels was analyzed via valproate level vs. ALT/AST levels and valproate dose vs. ALT/AST levels. No significant effect of valproate level was seen in AST and ALT levels. However, there was a significant effect on valproate dose on both AST ($p = 0.002$) and ALT ($p = 0.023$) in all patients and within both pediatric and adult arms. Of note is that although these results were statistically significant, they are still within the normal range for both groups.

Discussion

The goal of the study was to evaluate CBD for potential interactions with AEDs typically used for seizure control in patients with epilepsy. As such, several statistically significant interactions were identified in these analyses. Serum levels of *N*-desmethylclobazam, topiramate, eslicarbazepine, zonisamide, and rufinamide increased after CBD was started.

As described previously,[24] our study showed that CBD has a clinically and statistically significant interaction with clobazam and its active metabolite *N*-desmethylclobazam, resulting in increased sedation in adult participants. This interaction was noted despite study clinicians decreasing the clobazam dose (sometimes aggressively) in the presence of sedation. This aggressive decrease in clobazam dose is the explanation for the significant decrease in clobazam level with increasing CBD dose in the Mixed Procedure analysis. However, when separating those participants whose clobazam dose was decreased at the time of first two serum AED levels were obtained, a significant increase in clobazam levels was seen—levels increased significantly above the upper limit of normal. The interaction between CBD and *N*-desmethylclobazam appears much more profound, though, and this is likely explained by CBD's potent inhibition of CYP2C19, which is primarily responsible for the metabolism of *N*-desmethylclobazam.[29] This pharmacokinetic interaction results in effective prolongation of desmethylclobazam's half-life, and thus accumulation resulting in increased levels and increased incidence of sedation. The dosing of clobazam may need to be adjusted when starting CBD in anticipation of the increase of desmethylclobazam level and associated increases in the incidence of sedation. Of additional interest is the finding that our analysis did not reveal a significant interaction between CBD and clonazepam. Although clobazam and

clonazepam undergo metabolism via similar pathways, perhaps the structural differences between the two (clonazepam being a 1,4-benzodiazepine and clobazam being a 1,5-) may explain the difference, or a clonazepam metabolite (not measured in this study) is also increasing in level. However, this would not be clinically significant as all metabolites of clonazepam are inactive.[30]

Other findings were the significant increases in the levels of topiramate in both pediatric and adult participants and zonisamide in the adult participants. Topiramate is metabolized by CYP2C9 and CYP2C19, whereas zonisamide is metabolized by CYP3A4 and *N*-acetyltransferase.[22,31–34] CBD has shown inhibitory action on all CYP enzymes involved in the metabolism of these drugs, which could be the explanation for the observed interaction. Of additional interest is the noted interaction between CBD and zonisamide in the adult arm only. A pharmacokinetics study[34] on zonisamide monotherapy in children showed that plasma zonisamide levels linearly increased with age. Although this study included only pediatric participants, these findings could be extrapolated to adults and may explain our study's findings.

We do not have a clear explanation for the other interactions noted in the study between CBD and eslicarbazepine and rufinamide. Eslicarbazepine is metabolized via glucuronidation,[35] and rufinamide via carboxyl esterases.[36] Perhaps the delivery vehicle (sesame oil) in this formulation of CBD could be contributing to these interactions. Of note, sesamin (the major constituent in sesame seeds and oil) is known to block the activation of the pregnane X receptor (PXR), which has been shown to regulate CYP3A4, glutathione S-transferases, sulfotransferases, and uridine diphosphate-glucoronyltransferases, which may play a role in our observed interactions.[37]

An interaction was noted in those participants taking concomitant valproate and CBD with regard to elevated liver function test results. This observation was made despite there not being a significant change in the valproate levels with increasing CBD dose. In some cases, valproate dose was weaned or completely discontinued due to increasing or abnormally high AST and/or ALT levels after CBD treatment initiation. These abnormalities were not seen in participants who were not taking valproate in the study, indicating that there was an effect of the combined valproate and CBD on liver functions or that CBD affected the negative effects of valproate on liver functions. This emphasizes the need for not only selected drug levels to be monitored during therapy with CBD, but also for routine liver function test analysis in those patients who are taking concomitant valproate. Of clinical interest, after data collection for these analyses was complete, the four children whose valproate and CBD had to be discontinued due to abnormal liver test results were rechallenged on CBD alone and have not had recurrence of these abnormalities.

There were several limitations to our analyses. Although the data presented represent one year's worth of data collection, the sample sizes of patients taking each individual AED were relatively small, which in turn could be masking other potential interactions with CBD. We believe this was offset by the large number of data points (observations) within each subject, as blood levels were collected at almost every study visit (Table 2). In addition, due to the naturalistic design of the study, there was significant noise in the data that could not completely be accounted for in our analyses.

To summarize, this study introduces potential pharmacokinetic interactions between CBD and other commonly used AEDs in the treatment of epilepsy. Because CBD continues to be studied as a potential anticonvulsant, clinicians and researchers alike should be aware of significant changes in serum levels of clobazam/desmethylclobazam, eslicarbazepine, rufinamide, topiramate, and zonisamide. In addition, although this is part of routine drug monitoring, liver function should be monitored closely in patients taking concomitant CBD and valproate, as this combination may result in an increase in both AST and ALT levels. Going forward, formal pharmacokinetic studies under controlled conditions will be needed to further confirm these interactions.

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Conflict of Interest

Tyler Gaston, E. Martina Bebin, Gary Cutter, Yuliang Liu, and Jerzy Szaflarski have received salary support from the State of Alabama ("Carly's Law") for their work on this project. E. Martina Bebin and Jerzy Szaflarski have received consulting fees from Greenwich Biosciences, Inc. 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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