FULL-LENGTH ORIGINAL RESEARCH

# Drug–drug interaction between clobazam and cannabidiol in children with refractory epilepsy

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## Summary

**Objective:** **Under an expanded access investigational new drug (IND) trial, cannabidiol (CBD) is being studied as a possible adjuvant treatment of refractory epilepsy in children. Of the 25 subjects in the trial, 13 were being treated with clobazam (CLB). Because CLB and CBD are both metabolized in the cytochrome P450 (CYP) pathway, we predicted a drug–drug interaction, which we evaluate in this article.**

**Methods:** **Thirteen subjects with refractory epilepsy concomitantly taking CLB and CBD under IND 119876 were included in this study. Demographic information was collected for each subject including age, sex, and etiology of seizures, as well as concomitant antiepileptic drugs (AEDs). CLB, *N*-desmethylclobazam (norclobazam; nCLB), and CBD levels were measured over the course of CBD treatment. CLB doses were recorded at baseline and at weeks 4 and 8 of CBD treatment. Side effects were monitored.**

**Results:** **We report elevated CLB and nCLB levels in these subjects. The mean (± standard deviation [SD]) increase in CLB levels was 60 ± 80% (95% confidence interval (CI) [−2–91%] at 4 weeks); the mean increase in nCLB levels was 500 ± 300% (95% CI [+90–610%] at 4 weeks). Nine of 13 subjects had a >50% decrease in seizures, corresponding to a responder rate of 70%. The increased CLB and nCLB levels and decreases in seizure frequency occurred even though, over the course of CBD treatment, CLB doses were reduced for 10 (77%) of the 13 subjects. Side effects were reported in 10 (77%) of the 13 subjects, but were alleviated with CLB dose reduction.**

**Significance:** **Monitoring of CLB and nCLB levels is necessary for clinical care of patients concomitantly on CLB and CBD. Nonetheless, CBD is a safe and effective treatment of refractory epilepsy in patients receiving CLB treatment.**

**KEY WORDS:** **Antiepileptic drugs, Cannabis, Treatment-resistant epilepsy, Cytochrome P450 pathway, Norclobazam.**

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## Key Points

- When treating pediatric refractory epilepsy with both clobazam (CLB) and cannabidiol (CBD), levels of the active metabolite of CLB, N-desmethylclobazam (norclobazam; nCLB) can significantly increase.
- Monitoring of CLB and nCLB levels is necessary for clinical care of patients concomitantly on CLB and CBD.
- CBD is a safe and effective treatment of refractory epilepsy in patients on CLB treatment.

Refractory epilepsy is a serious condition that occurs in one third of patients with epilepsy. Thus, there is a need for exploration of additional treatment options. Cannabidiol (CBD) is a major chemical of marijuana that does not possess psychoactive properties. Anecdotal and survey evidence[1] and data from preclinical[2–9] and clinical[10,11] trials have indicated that CBD might have safe and effective antiepileptic properties comparable to U.S. Food and Drug Administration (FDA)–approved antiepileptic drugs (AEDs).[2–5] Subsequently, an ongoing Massachusetts General Hospital (MGH) Institutional Review Board (IRB)–approved clinical trial under the expanded access investigational new drug (IND) 119876 from the FDA is studying the safety and efficacy of cannabidiol (CBD) (Epidiolex; GW Pharmaceuticals) as a new adjuvant treatment for refractory epilepsy in 25 children.

Thirteen of these 25 children with refractory epilepsy were being treated with clobazam (CLB), which was first approved by the FDA in 2011 for the treatment of Lennox-Gastaut syndrome (LGS) and later for refractory epilepsy.[12] Common side effects include drowsiness, ataxia, irritability, restlessness, urinary retention, tremor, and loss of appetite.[12]

Both CBD and CLB are metabolized by the cytochrome P450 (CYP) pathway. Important hydroxylations of CBD metabolism are catalyzed by CYP 2C19 and CYP 3A4,[13] and recent studies have indicated that CBD is a potent inhibitor of both enzymes.[14,15] CLB metabolism similarly involves CYP 3A4, the primary enzyme in its metabolic pathway, and, to a lesser extent, CYP 2C19. Both of these enzymes catalyze the metabolism of *N*-desmethylclobazam (norclobazam; nCLB), the active metabolite of CLB,[12,16,17] which in animal and in vitro studies have shown to be about 20–100% as potent as CLB.[12]

The elimination half-lives of CLB and nCLB are 36–42 and 71–82 h, respectively.[12] Although CLB and nCLB clearances are lower in geriatric patients (>64 years old), there is no significant difference in clearance between other age groups or between sexes.[12] A review of 132 papers analyzing CBD use alone in humans and animals reported an average elimination half-life of 24 h.[18]

Because the trial subjects have refractory epilepsy, many are taking multiple concomitant AEDs. Pharmacokinetic analysis of CLB in previous clinical trials has demonstrated that there is a clinically significant drug–drug interaction when CLB is taken with strong or moderate CYP 2C19 inhibitors (e.g., sulthiame [STM] and stiripentol [STP];[19,20] valproic acid [VPA], by contrast, is a weak inhibitor).[21] In addition, STP has been shown to inhibit CYP 3A4, potentially affecting CLB metabolism.[22] Although a recent retrospective study has shown that CYP 3A4 inducers phenobarbital (PB), phenytoin (PHT), and carbamazepine (CBZ) significantly reduce serum CLB concentrations,[22] clinical trials have demonstrated that there is no clinically significant drug–drug interactions when CLB is taken with CYP 3A4 inducers, CYP 2C9 inducers (e.g., PB, PHT, and CBZ), or CYP 2C9 inhibitors (e.g., FLB and oxcarbazepine [OXC]).[12,22] Studies have also shown that there are no drug–drug interactions between CLB and various other drugs that are also CYP 2C19 or CYP 3A4 substrates.[22,23]

In this article we evaluate the interaction between CBD and CLB in the 13 children in this current trial who are taking both drugs concomitantly.

## Methods

### Clinical protocol

Thirteen subjects (age range, 4–19 years old; mean, age 11) with refractory epilepsy concurrently taking CLB and CBD under IND 119876 were included in this study. Demographic information was collected for each subject including age, sex, and etiology of seizures, as well as concomitant AEDs. Drug levels of these concomitant AEDs were also monitored and other AED–CBD interactions are currently being evaluated as part of a larger data analysis.

Patients began taking CBD at a dose of 5 mg/kg/day and titrated up by 5 mg/kg/day each week to a goal of 25 mg/kg/day. Throughout the study, CLB doses were either kept constant or decreased when side effects were observed. CLB doses were recorded and plasma levels of CLB, nCLB, and CBD were measured at baseline and at weeks 4 (CBD dose = 20 mg/kg/day) and 8 (25 mg/kg/day) of CBD treatment. CBD dose was decreased for subject 1 from 25 to 20 mg/kg/day at week 4. CLB and nCLB blood samples were collected at least a week after CBD dose increase for week 4 levels and a month after CBD dose increase for week 8 levels. No de-challenge of CBD was performed. CLB dose adjustments were made at least a week before CLB and nCLB blood levels were drawn, with the exception of three subjects: Subject 3 had a CLB dose adjustment 3 days before week 8 levels were drawn, subject 16 had a CLB dose adjustment 5 days before week 4 levels were drawn, and subject 19 had a CLB dose adjustment a day before week 4 levels were drawn. Because of laboratory errors (blood was not drawn in a sodium heparin tube as required for testing), CBD levels were unavailable for subjects 2, 6, and 11 at

week 4. Subject 5 was no longer taking CLB at week 8; therefore, CLB and nCLB levels were not measured.

Subjects and/or their caregivers were interviewed (in person, phone, or email) in weekly safety evaluations about possible side effects during CBD treatment. They were also instructed to call the research nurse as needed. CBD compliance was determined at each visit by comparing actual and expected volumes of CBD used; CLB compliance was determined by subject self-reported dosing. For each subject, seizure frequency was measured at baseline (based on the previous 28 days) and week 8 (based on the previous 28 days, the duration of which the subjects was taking 25 mg/kg/day of CBD). Responder rate (>50% decrease in seizures) was calculated.

Percent increases of CLB and nCLB plasma levels were calculated from the highest level measured over the 8-week CBD treatment period for each subject. Percent decreases of CLB doses were calculated from the lowest dose recorded over the CBD treatment period for each subject. Means and standard deviations of percent increases of CLB and nCLB levels and percent decrease of CLB doses were determined.

### Plasma drug assay methodology

CLB and nCLB blood levels were analyzed at MEDTOX Laboratories though liquid chromatography with tandem mass spectrometry (LC-MS/MS) with a limit of detection (LOD) of 10 ng/ml for both analytes. MEDTOX Laboratories' reference ranges for CLB and nCLB are 30–300 and 300–3,000 ng/ml, respectively.

CBD blood levels were analyzed at GW Pharmaceuticals through ultra-performance liquid chromatography with tandem mass spectrometry (UPLC-MS/MS) with a lower limit of quantification (LLOQ) of 2.00 ng/ml.

### Statistical analysis

Empirical cumulative distribution graphs were made of the fold-elevation in levels of CLB and nCLB at weeks 4 and 8 of CBD treatment for subjects who reduced their CLB doses. Ninety-five percent confidence intervals (95% CI) for the fold-increase in CLB and nCLB levels were calculated from the empirical cumulative distributions (Fig. 2) in MATLAB using the Kolmogorov-Smirnoff confidence bands.

## Results

Table 1 presents the demographics, concomitant AEDs, change in seizure frequency, and side effects for each subject. Nine of 13 subjects had a >50% decrease in seizures, corresponding to a responder rate of 70%. The mean (± standard deviation [SD]) change in seizure frequency was a 51% decrease ± 56%. Only two subjects had an increase in seizure frequency during the treatment period (subjects 4 and 8, 14% and 99%, respectively). Both of these subjects had CLB dose reductions. Over the course of CBD treatment, CLB doses were reduced for 10 (77%) of the 13 subjects (Fig. 1). The mean change in seizure frequency for the 10 subjects with lowered CLB doses was a 50% decrease, whereas the mean change for those without was a 55% decrease.

Baseline CLB doses ranged from 0.18 to 2.24 mg/kg/day (mean, 1 mg/kg/day). Baseline CLB levels ranged from 54 to 1,000 ng/ml (mean, 340 ng/ml) (therapeutic range, 30–300 ng/ml). Baseline nCLB levels ranged from 97 to 19,000 ng/ml (mean, 3,000 ng/ml) (therapeutic range, 300–3,000 ng/ml). At week 4 of CBD treatment, plasma CBD levels ranged from 82 to 1,000 ng/ml (mean, 388 ng/ml). At week 8, plasma CBD levels ranged from 100 to 800 ng/ml (mean, 450 ng/ml).

Figure 1 illustrates the CLB, nCLB, and CBD blood levels for each individual subject in the study, as well as the CLB doses for each subject. Figure 2 shows the empirical cumulative distribution of the fold-elevation in levels of CLB and nCLB at weeks 4 and 8 of CBD treatment. In these

**Table 1. Subject demographics, etiology, AEDs, and change in seizure frequency**

| Subject | Age | Sex | Etiology | Concomitant AEDs | Change in Sz frequency | Side effects |
|---|---|---|---|---|---|---|
| 1[a] | 16 | M | Dravet syndrome | CLB, VPA | −81 | Restless sleep |
| 2[a] | 7 | F | Doose syndrome | CLB, VPA, RFN | −54 | None |
| 4 | 19 | M | Cortical dysgenesis | CLB, PHT, LCS | +14 | Ataxia, urinary retention |
| 5 | 14 | M | Isodicentric duplication chromosome 15q13 | CLB, VPA, LEV | −26 | Ataxia, tremor, loss of appetite |
| 6 | 8 | F | Dravet syndrome | CLB, FBM | −68 | Drowsiness, irritability |
| 8 | 13 | M | Cortical dysgenesis | CLB, LEV, LCS | +99 | Drowsiness |
| 10 | 16 | M | Cortical dysgenesis | CLB, ZNS | −74 | Drowsiness |
| 11 | 6 | F | *CDKL5* mutation | CLB, VGB | −100 | Drowsiness |
| 12 | 12 | M | Tuberous sclerosis complex | CLB, LTG | −58 | None |
| 13 | 5 | M | Tuberous sclerosis complex | CLB, LCS | −93 | Irritability |
| 14 | 8 | F | Lissencephaly | CLB, LEV, RFN | −94 | None |
| 16 | 12 | F | Doose syndrome | CLB, LCS, LTG | −100 | Drowsiness |
| 19[a] | 4 | F | Dravet syndrome | CLB | −30 | Drowsiness |

AED, antiepileptic drug; VPA, valproic acid; RFN, rufinamide; PHT, phenytoin; LCS, lacosamide; LEV, levetiracetam; FBM, felbamate; ZNS, zonisamide; VGB, vigabatrin; LTG, lamotrigine; sz, seizure.
[a]Did not change CLB dose.

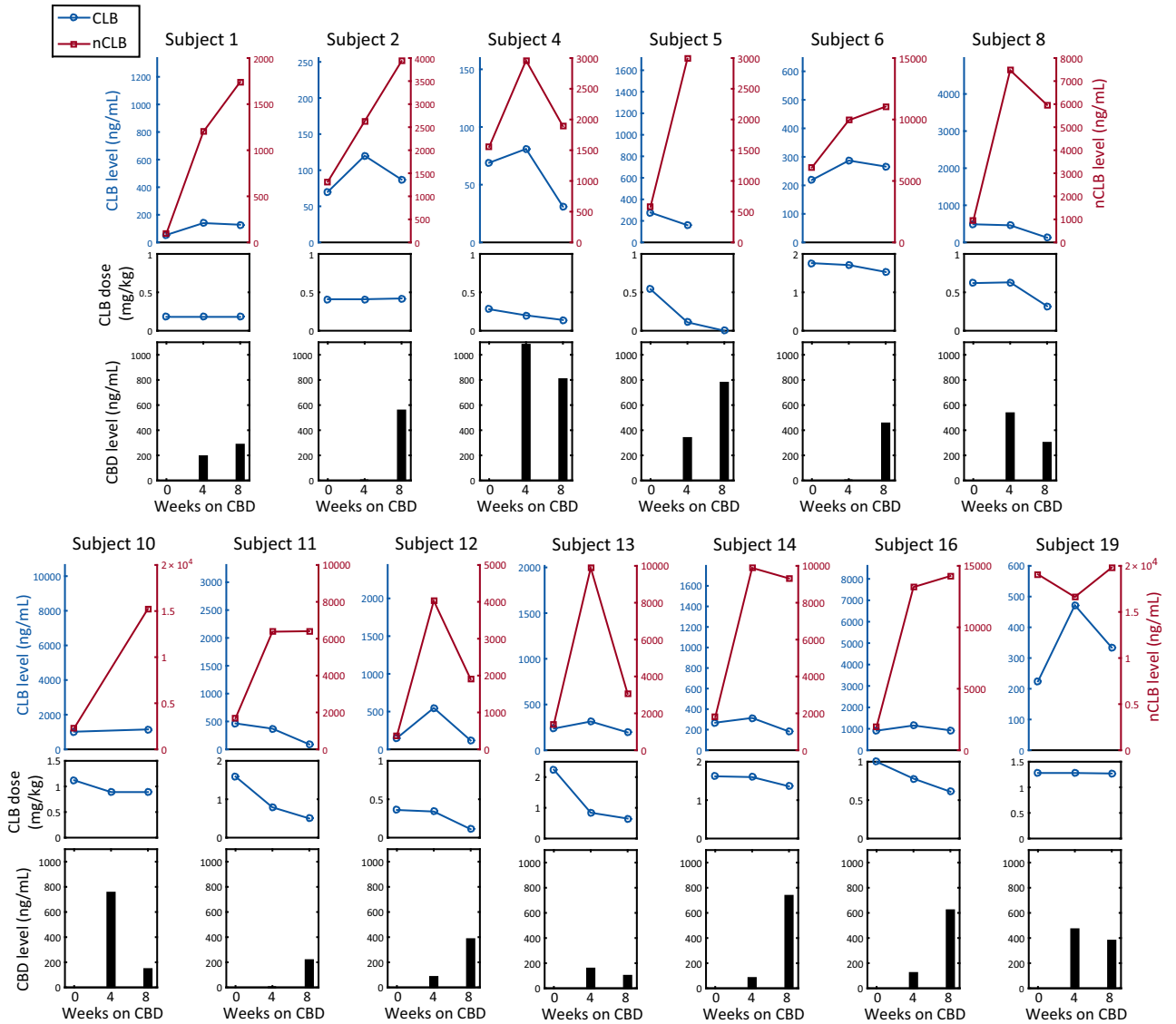


**Figure 1.**

Norclobazam (nCLB), the active metabolite of clobazam (CLB), increased substantially in 12 of 13 subjects on 20–25 mg/kg cannabidiol (CBD). Plasma levels of CLB and nCLB are shown for each subject (top panels) at baseline and after 4 and 8 weeks of CBD administration. CBD dose was 20 mg/kg at week 4 and 25 mg/kg (20 mg/kg for subject 1) at week 8 (plasma levels are shown in the lower panels). CLB oral doses were decreased in 10 of 13 subjects (middle panels). Note that the vertical scaling is done independently for each subject to emphasize relative changes.



plots, the y-value (vertical axis) describes the fraction of subjects with a fold-increase in nCLB greater than or equal to the value of the x-value (horizontal axis).

The mean increase of CLB levels was 60 ± 80%, which was not statistically significant; the 95% confidence interval (CI) of fold-elevation in CLB levels was (0.98–1.91) at week 4 and (0.56, 1.21) at week 8 (Fig. 2). In every subject (except subject 5, whose CLB dose was reduced to 0), the nCLB level after 8 weeks of CBD was higher than at the start, despite the reduction in CLB dose. The mean increase in nCLB levels was 500 ± 300%, a substantial change that was clearly significant using the Kolmogorov-Smirnoff confidence band (Fig. 2). The 95% CI of fold-elevation in nCLB levels was (1.9, 7.1) at week 4 and (2.17, 6.33) at week 8. That is, with a confidence of 95%, there was at least a 1.9-fold increase in nCLB levels, even though most of the patients had reduced their CLB doses (Fig. 2).

Side effects were reported in 10 (77%) of the 13 subjects (Table 1). These 10 subjects experienced drowsiness (n = 6), ataxia (n = 2), irritability (n = 2), restless sleep (n = 1), urinary retention (n = 1), tremor (n = 1), and loss of appetite (n = 1). Although some subjects improved without a significant change in nCLB levels, subjects with low-

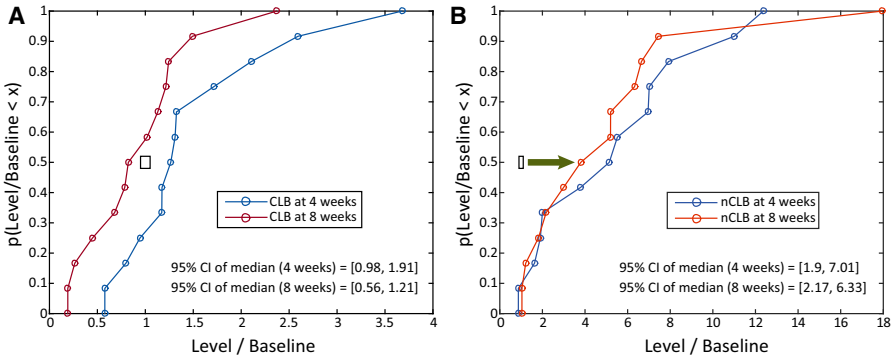


**Figure 2.**
Empirical cumulative distributions of the fold-elevation in levels of CLB (**A**) and nCLB (**B**). Shown at 4 and 8 weeks of CBD treatment; data for all patients with reduced oral doses of CLB are included. The rectangle indicates the expected median value with no change. Ninety-five percent confidence intervals (95% CIs) for the fold-increase in CLB and nCLB levels were calculated from the empirical cumulative distributions in MATLAB, using the Kolmogorov-Smirnoff confidence bands.


ered nCLB levels improved; moreover, subjects that did not experience a reduction in nCLB levels (with the exception of Subject 10) experienced a reduction in CLB levels. Regardless, all side effects were resolved with CLB dose adjustments. All study subjects continued to tolerate CBD well at time of data analysis (week 36 of treatment).

## Discussion

These results illustrate an interaction between CLB and CBD. As shown in Figures 1 and 2, nCLB levels were much more affected by CBD than were CLB levels. The mean increase of nCLB levels was 500 ± 300%, whereas the mean increase of CLB levels was 60 ± 80%. Despite the reduction of CLB doses during the treatment period, a 95% CI demonstrated an approximately two- to sixfold elevation in nCLB levels at week 8 as compared to baseline levels (Fig. 2).

The side effects reported in 10 (77%) of the 13 subjects are all commonly seen in patients with high CLB doses (Table 1) and were alleviated with CLB dose reduction despite a persistence of high nCLB levels, but corresponding to a reduction in CLB and/or nCLB levels in all but one subject (subject 10) (Figs. 1 and 2). Future studies should observe longitudinal nCLB levels after dose reduction to determine when they normalize.

CBD inhibits CYP 2C19 and CYP 3A4, which catalyze the metabolism of nCLB.[14–17] This inhibition likely leads to an accumulation of nCLB, which studies have shown to be about 20–100% as potent as CLB.[12] In addition, genetic polymorphism exists for CYP 2C19 expression, resulting in rare poor CYP 2C19 metabolizers,[24] in which plasma levels of *N*-desmethylclobazam are fivefold higher in plasma than in CYP 2C19 extensive metabolizers.[12] These data further support our hypothesis that elevated nCLB levels in our subjects were due to CBD inhibition of CYP 2C19. CYP 2C19 polymorphisms may also explain varying levels of CLB and nCLB, CLB-to-nCLB ratios, and responses to CBD.

CBD levels do not appear to correlate with CLB or nCLB levels, suggesting that CLB does not affect the metabolism of CBD (Fig. 1). Responder rate was 70% and subjects experienced a mean decrease in seizure frequency of 51% during CBD treatment. Elevated nCLB levels (approximately 2–6 times expected values at a 95% confidence level) may have counteracted the potential negative effects of CLB dose reductions (Fig. 2). Mean percent change in seizure frequency for subjects whose CLB doses were not reduced (50% decrease in seizure frequency) was similar to that of subjects whose CLB doses were reduced (55% decrease).

Given the half-lives of CBD, CLB, and nCLB (at least a day),[12,18] levels were not likely significantly affected by variable relationship of time between CLB and CBD doses and blood draw. Limitations of possible noncompliance do exist, particularly given that CLB compliance is self-reported. In addition, limitations of this study include small sample size, limited observation period, and possible confounding factors of concomitant AEDs.

In conclusion, there is a drug–drug interaction between CLB and CBD. Nonetheless, reduction of CLB dose alleviates consequential side effects and all subjects continued to tolerate CBD well at time of data analysis (week 36 of treatment). Observation of nCLB levels is important in clinical treatment of patients concomitantly on CBD and CLB. CBD appears to be safe and effective in pediatric patients on CLB treatment for refractory epilepsy. Further studies of tolerability and efficacy are warranted.

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## Disclosure of Conflict of Interest

Elizabeth A. Thiele received the study medication from GW Pharmaceuticals and has received unrestricted educational grants from Lundbeck Pharmaceutical Company. The remaining authors have no conflicts of interest.

## Ethics Statement

This study is consistent with *Epilepsia* and the guidelines for ethical publication from the Committee on Publication Ethics (COPE).

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