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Drug–drug interactions and pharmacodynamics of concomitant clobazam and cannabidiol or stiripentol in refractory seizures

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ABSTRACT

Objective: The goal of this study was to characterize the drug–drug interactions between clobazam and 2 antiseizure drugs, cannabidiol and stiripentol, for treatment of refractory seizures through the use of pharmacokinetic modeling.

Methods: A population pharmacokinetic/pharmacodynamic model was developed to characterize the combined effect of clobazam and its active metabolite, *N*-desmethylclobazam (i.e., *N*-clobazam), on seizure protection in patients with Lennox–Gastaut syndrome using data from the phase 3 CONTAIN trial. Drug–drug interactions between clobazam and cannabidiol were examined by comparing model-generated data to data from a study of 13 patients taking concomitant clobazam and cannabidiol. Modeling data were also descriptively compared with studies of patients administered both clobazam and stiripentol. Sedation-related adverse events from CONTAIN were analyzed to determine the exposure–somnolence relationship of clobazam.

Results: Exposure-efficacy analysis from the pharmacokinetic/pharmacodynamic model using CONTAIN data indicated that clobazam (half-maximal effective concentration [EC_{50}], 303 ng/mL) was 3 times more potent than *N*-clobazam (EC_{50}, 899 ng/mL). After administration of clobazam, when both clobazam and *N*-clobazam concentrations were each 1 to 2 times the EC_{50} value (clobazam dose, 20 mg), 70.0%–74.9% seizure protection was predicted; when concentrations were >2 times the EC_{50} value (clobazam dose, 40 mg), 74.0%–96.9% seizure protection was predicted. Generalized additive model analyses demonstrated decreased seizure probability with higher plasma concentration of clobazam. Coadministration of stiripentol and clobazam resulted in increased respective median plasma concentrations of clobazam and *N*-clobazam (1.1–1.2 times and 5.2–8.2 times) compared with administration of placebo and clobazam. Probability of somnolence significantly increased with age and higher *N*-clobazam plasma concentration.

Significance: Awareness of drug–drug interactions between clobazam and cannabidiol is needed when adding cannabidiol or stiripentol to a regimen of clobazam or vice versa. Based upon our population pharmacokinetic/pharmacodynamic model, we predict that an increase in *N*-clobazam levels, which patient data show may enhance efficacy and/or make adverse events such as somnolence more likely.

1. Introduction

Clobazam (CLB) is approved by the US Food and Drug Administration (FDA) as an adjunctive therapy for seizures associated with Lennox–Gastaut syndrome (LGS) in patients aged ≥2 years [1]. Multiple antiepileptic medications (AEMs) are often needed to manage treatment-refractory seizures in patients with LGS and Dravet syndrome [2,3]. Epidiolex (Cannabidiol (CBD)) was recently approved by the FDA to treat seizures associated with LGS and Dravet syndrome in patients aged ≥2 years [4]. In the pivotal phase 3 clinical trials and in an open-label, expanded access trial of CBD as adjunctive treatment for

Abbreviations: AE, adverse event; AEM, antiepileptic medication; CBD, cannabidiol; CI, confidence interval; CLB, clobazam; C_{min}, minimum blood plasma concentration; C_{max}, peak plasma level; CYP, cytochrome P450; DDI, drug–drug interaction; EC_{50}, half-maximal effective concentration; FDA, US Food and Drug Administration; GABA, gamma-aminobutyric acid; K_i, binding affinity; LGS, Lennox–Gastaut syndrome; *N*-CLB, *N*-desmethylclobazam; NONMEM, nonlinear mixed-effect modeling; OR, odds ratio; PBO, placebo; PD, pharmacodynamic; PK, pharmacokinetic; PopPK, population pharmacokinetic; SE, standard error; STP, stiripentol; VPA, valproic acid.

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refractory seizures, 47% to 65% of patients were receiving CLB as a concomitant medication [5–8].

Clobazam and its active metabolite, *N*-desmethylclobazam (*N*-CLB), are metabolized in the liver by several cytochrome P450 (CYP) isozymes. In particular, the parent molecule (CLB) is metabolized by CYP3A4 and CYP2C19 to *N*-CLB, which is then further metabolized by CYP2C19 to an inactive metabolite [9,10]. Cannabidiol is hepatically metabolized by several CYP isozymes, primarily CYP2C19 and CYP3A4, with CYP1A1, CYP1A2, CYP2C9, and CYP2D6 contributing as well [11]. Cannabidiol also inhibits CYP2C19 as well as CYP3A4, CYP3A5, and CYP2D6 [12–14]. As a result, the concomitant use of CLB with CBD increases the serum concentration of *N*-CLB and possibly CLB, as demonstrated by several open-label studies examining concomitant use of both CLB and CBD [15–17]. This could result in increased efficacy or a more frequent occurrence of adverse events (AEs) in comparison with either medication alone [16,18]. There is little published concentration-effect data for CBD or prospective pharmacodynamic (PD) analysis of the observed pharmacokinetic (PK) interaction between CBD and CLB. A PK analysis of drug–drug interactions (DDIs) between CLB and CBD may provide important insight that will facilitate future work aimed at ensuring patient safety and treatment optimization.

Drug–drug interactions have also been reported with the concomitant use of CLB and another CYP inhibitor stiripentol (STP), which is approved in the United States, Europe, and Canada for adjunctive treatment of patients with Dravet syndrome not controlled with valproate and CLB [19–22]. Stiripentol undergoes extensive metabolism involving CYP2C19, CYP3A4, and CYP1A2; displays nonlinear PK; and inhibits CYP3A4, CYP1A2, and CYP2C19 [22–25]. A previous population PK (PopPK) model of CBD and *N*-CLB plasma levels in patients ≥3 years old demonstrated CLB/*N*-CLB ratios 2 to 3 times higher than published values for patients taking CLB and STP, indicating that STP may increase *N*-CLB levels [21,26]. Evaluation of potential DDIs between CLB and STP may provide additional insight into the effects of concomitant CLB and other AEMs that potently inhibit CYP isoforms.

The goals of this study were (1) to characterize the DDIs between CBD and CLB, determine the effect of CBD on *N*-CLB levels, and examine the possible clinical implications on efficacy and AEs when CBD and CLB are used concomitantly; and (2) to examine the effect of STP CYP inhibition on CLB PK/PD relationships.

2. Methods

Nonlinear mixed-effect modeling (NONMEM) of patient data was used to evaluate the exposure–efficacy relationship of CLB using data from the phase 3 CONTAIN trial (NCT00518713) of adjuvant CLB in the treatment of patients with LGS [27]. The study protocol was approved by local institutional review boards or independent ethics committees. Patients with a ≥25% reduction in drop seizures from baseline to the end of the maintenance period were considered treatment responders. An exposure–response PopPK/PD model (incorporating placebo effect) that accounts for competitive agonism between CLB and its active metabolite was developed to characterize the combined effect of CLB plus *N*-CLB in patients with LGS treated with CLB. A similar approach characterizing DDIs with CLB and other AEMs, which inhibit specific CYP isozymes, and simulating plasma concentrations of both CLB and *N*-CLB using data from the phase 3 CONTAIN study and from a phase 1 bioavailability study, has been previously described and validated [28]. After incorporating the time course of the placebo response and associated population fixed effects parameter estimates into the PopPK/PD model, the exposure–response relationships for both CLB and *N*-CLB in the presence of CBD (GW Pharmaceuticals, Cambridge, UK) were estimated. As both CLB and *N*-CLB have separately been identified as having pharmacologic activity [29], a standard PD model for competitive agonism was implemented to quantify the effect of both entities plus CBD on seizure rate [30]. The drug effect model is shown in Fig. 1. Using the estimates of the parameters of the above model, the relative contributions of CBD, CLB, and *N*-CLB were determined.

To investigate the effect of DDIs between CLB and CBD, PK and efficacy data predicted using the PopPK model of both CLB and *N*-CLB exposures were compared with findings from a previously published open-label study of 13 patients with refractory epilepsy who had CBD added to an existing CLB regimen (Fig. 2A) [9]. Clobazam, *N*-CLB, and CBD PK data were taken from the published article for use in the current analysis. Patients in the CBD and CLB study with a ≥50% reduction in drop seizures were considered responders [9]. Generalized additive modeling and 2-step Firth logistic regression analyses were conducted to determine the effect of CBD, CLB, and *N*-CLB concentrations on seizure response, as well as the effects of age and sex. Population PK model-predicted data for CLB/*N*-CLB were also descriptively compared with data from several randomized, double-blind clinical trials examining the concomitant use of CLB and STP (Fig. 2B) [19,21].

Patients who experienced sedation-related AEs in the phase 3 CONTAIN trial were included in an analysis of the exposure–somnolence relationship of CLB (Fig. 2C). This relationship was evaluated using penalized logistic regression (i.e., shrinkage) and the Bayesian model averaging approach. These strategies reduce the variability of problematically unstable parameter estimates that are associated with a relatively flat likelihood of event occurrence (introducing a small amount of bias) [31] and address model uncertainty, respectively. Sedation-related AEs included hypersomnia, lethargy, sedation, and somnolence.

3. Results

Data from 202 patients with evaluable PK and efficacy were utilized in the model; 145 patients received CLB (0.25 mg/kg/day [maximum of 10 mg/day], 0.5 mg/kg/day [maximum of 20 mg/day], or 1 mg/kg/day [maximum of 40 mg/day]), and 57 received placebo. Patients with PK concentrations that were discordant with the temporal nature of their profiles, patients who were not part of the modified intent-to-treat analysis population, and patients for whom PK parameters could not be estimated were excluded from the analysis.

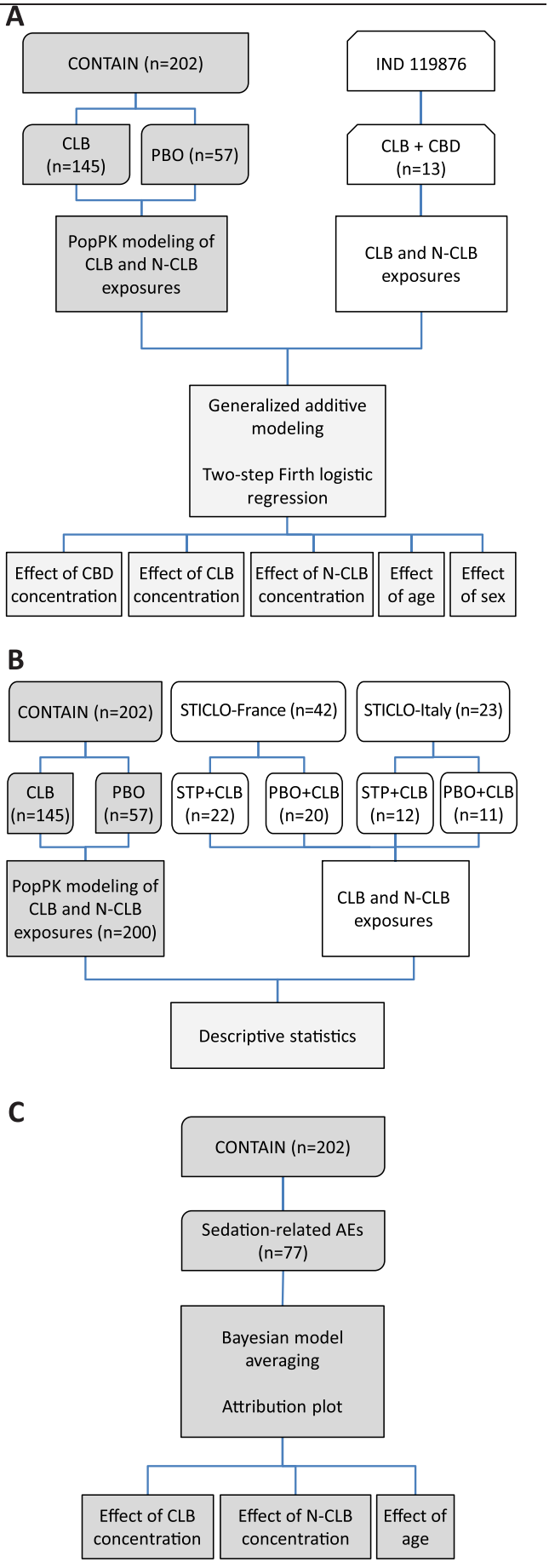
3.1. Pharmacokinetics and efficacy

An exposure–efficacy analysis indicated that CLB (half-maximal effective concentration [EC_{50}], 303 ng/mL) was 3 times more potent than *N*-CLB (EC_{50}, 899 ng/mL). This potency difference is consistent with the difference in the binding affinities (K_i) between CLB and *N*-CLB for gamma-aminobutyric acid (GABA) receptors (equipotent to one-fifth as potent) [1,32].

Clobazam and *N*-CLB concentrations that are each 1 to 2 times their respective EC_{50} values after administration of CLB 20 mg are predicted to yield 70.0% to 74.9% seizure protection; this increases to 74.0% to

$$E = E_{max} \times \left(\frac{C_{avg},p}{EC_{50},p \times \left(1 + \frac{C_{avg},m}{EC_{50},m}\right) + C_{avg},p} + \frac{C_{avg},m}{EC_{50},m \times \left(1 + \frac{C_{avg},p}{EC_{50},p}\right) + C_{avg},m} \right)$$

Fig. 1. Competitive agonism model for CLB PopPK. *E* indicates the reduction in seizures from baseline; E_{max} indicates the maximum seizure response; C_{avg} indicates the average plasma concentration of either the parent compound, CLB, or the metabolite, *N*-CLB; EC_{50} indicates the half-maximal effective concentration. CLB = clobazam; m = metabolite; *N*-CLB = *N*-desmethylclobazam; p = parent; PopPK = population pharmacokinetics.



96.9% at CLB concentrations that are greater than 2 times the EC_{50} (40 mg).

3.2. How cannabidiol affects clobazam and N-clobazam

Average CLB and *N*-CLB concentrations after add-on CBD treatment [9] were separately compared with PopPK model-predicted concentrations. The average steady-state CLB concentration after add-on CBD treatment was similar to PopPK model-predicted concentrations with a CLB dosage of 0.5 mg/kg/day (245.0 vs 246.7 ng/mL). A comparison of the average steady-state concentrations of CLB after add-on CBD treatment and the PopPK model-predicted steady-state concentrations for doses of 1.5 and 2 mg/kg is shown in Fig. 3A. However, the average steady-state *N*-CLB concentration during CBD treatment was higher, in the range of model-predicted concentrations with CLB dosages of 1.5 to 2 mg/kg/day (Fig. 3B).

3.3. How stiripentol affects clobazam and N-clobazam

In 2 studies in which STP was coadministered with CLB, median plasma concentrations of CLB were increased by 1.1 to 1.2 times compared with the administration of placebo and CLB [19]. Median plasma concentrations of *N*-CLB were increased by 5.2 to 8.2 times in patients receiving STP (mean dosage, 48.9–50.6 mg/kg/d) and CLB (mean or median dosage, 0.5 mg/kg/d) compared with patients receiving placebo and CLB [19]. These higher relative plasma concentrations of *N*-CLB compared with CLB in patients receiving STP resulted in lower CLB to *N*-CLB ratios for patients receiving both STP and CLB than those receiving placebo and CLB (Table 1) [19].

Taking into account between-group differences for STP and CLB compared with placebo and CLB, response rates among patients receiving STP and CLB were similar to PopPK model-predicted response rates to CLB (57.6%–66.4% vs 68.3%) [19]. However, the mean (STICLO-France) and median (STICLO-Italy) CLB dosages in the STP and CLB studies were much lower than the PopPK-modeled CLB dosage (0.52 and 0.5 mg/kg/day, respectively, vs 1.5 to 2 mg/kg/day) [19].

3.4. Pharmacokinetics and somnolence

Data from 77 patients in the CONTAIN trial who experienced sedation-related AEs were used in this analysis. *N*-Desmethylclobazam concentration and age were significant predictors of somnolence (Table 2), with the probability of somnolence increasing with age and higher *N*-CLB plasma concentration (Fig. 4). Patients aged ≤18 years had a ≤30% probability of experiencing somnolence. Bayesian model averaging found that *N*-CLB concentration and age, but not CLB concentration, were significant variables in predicting somnolence. These variables accounted for 66% of the probability of a patient experiencing somnolence due to CLB.

4. Discussion

In 2011, CLB was approved by the FDA as an adjunctive treatment for seizures associated with LGS in patients ≥2 years of age [1]. Cannabidiol may be an effective therapy for treatment-refractory seizures and drop seizures and was recently approved by the FDA to treat seizures associated with LGS or Dravet syndrome in patients ≥2 years of age [4–8]. Stiripentol has also recently received FDA approval for seizures associated with Dravet syndrome in patients ≥2 years of age who are receiving CLB [22]. Multiple AEMs are often used in combination to more

Fig. 2. Study design for (A) CLB and CBD DDIs, (B) STP and CLB DDIs, and (C) analyses of the AE of somnolence in the phase 3 CONTAIN study. AE = adverse event; CBD = cannabidiol; CLB = clobazam; DDI = drug–drug interaction; IND = investigational new drug; *N*-CLB = *N*-desmethylclobazam; PBO = placebo; PopPK = population pharmacokinetics; STP = stiripentol.

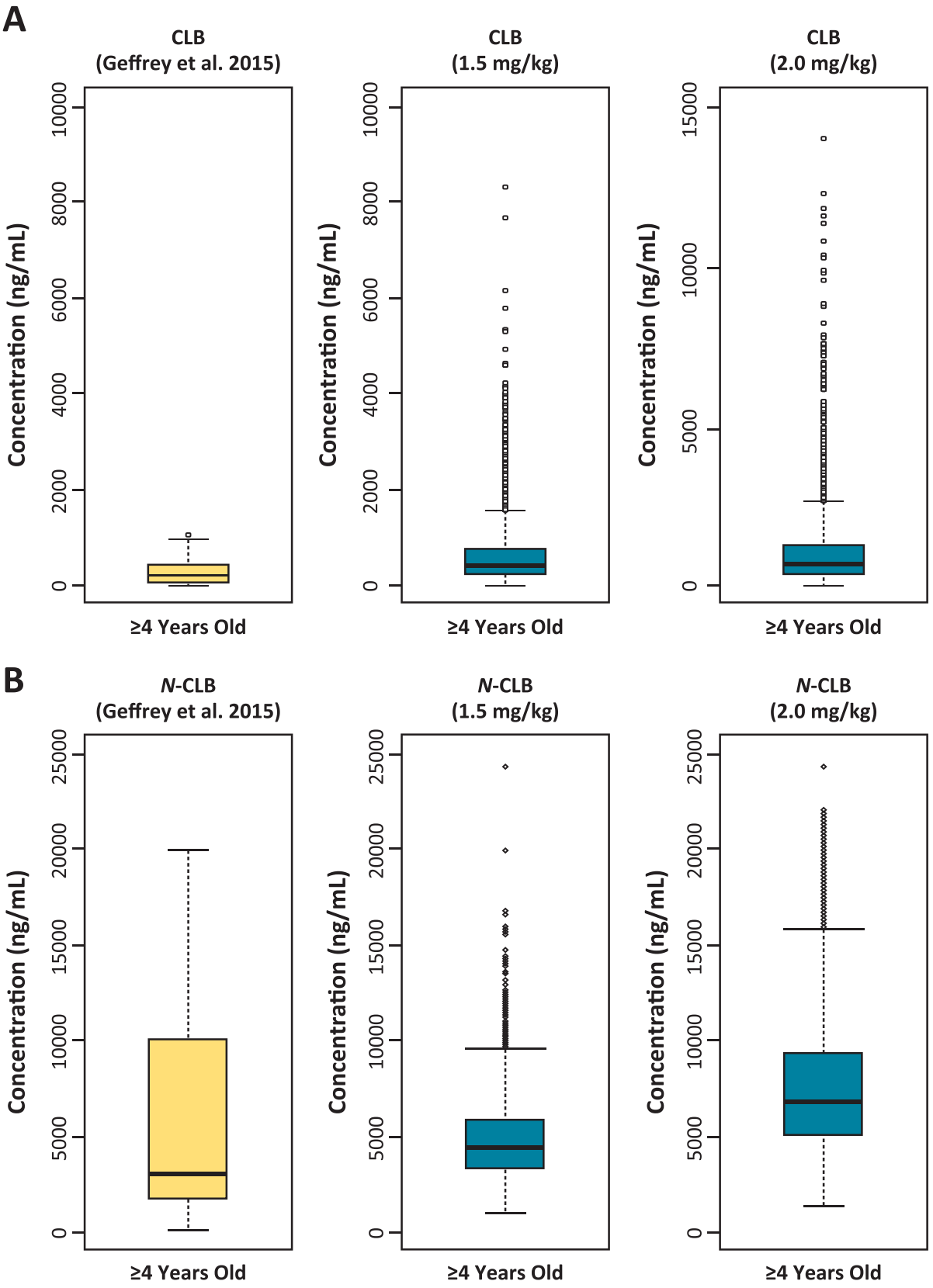


Fig. 3. Comparative distributions of (A) CLB and (B) *N*-CLB steady-state concentrations during add-on CBD treatment. The thick horizontal line within the box is the median concentration, and the ends of the box are the first quartile (lower end) and third quartile (upper end) values. The height of the box is the interquartile difference (IQD; i.e., the interval between the first and third quartile). The dotted lines extending beyond the box to the horizontal lines are the upper and lower adjacent values, which are the largest observation that is ≤to the upper quartile + 1.5 × IQD (upper adjacent value) or the smallest observation that is ≤to the lower quartile − 1.5 × IQD (lower adjacent value). The symbols above the upper adjacent values represent outside values and include both actual PK data points and modeled PopPK predicted values. CBD = cannabidiol; CLB = clobazam; *N*-CLB = *N*-desmethylclobazam; PK = pharmacokinetic; PopPK = population pharmacokinetic.

Table 1
Baseline characteristics and CLB/*N*-CLB concentrations in STP add-on studies compared with predicted concentrations.

	STICLO-France		STICLO-Italy		CONTAIN (PopPK)	
	PBO[a] n = 20	STP[a] n = 22	PBO[a] n = 11	STP[a] (50.6 mg/kg/day) n = 12	CLB (1.5 mg/kg/day) n = 200[b]	CLB (2.0 mg/kg/day) n = 200[b]
Diagnosis	DS	DS	DS	DS	LGS	LGS
Age range, y	3.2–20.7	3–16.7	3.5–18.9	3.7–15.5	≥3–16	≥3–16
Weight range, kg	15–70	14–60	18–49	16–55	10–69	10–70
CLB dosage, mean, mg/kg/day	0.48	0.52	0.50	0.50	1.5	2.0
CLB C_{min}, mean (95% CI), ng/mL	198[c]	244[c]	201[c]	225[c]	654 (93–2368)	1083 (134–3944)
N-CLB C_{min}, mean (95%CI), ng/mL	800[c]	4140[c]	490[c]	4010[c]	4780 (1998–9605)	7570 (2724–16,482)
CLB/*N*-CLB ratio	0.25	0.06	0.41	0.06	0.14	0.14

CI = confidence interval; CLB = clobazam; C_{min} = minimum blood plasma concentration; DS = Dravet syndrome; LGS = Lennox–Gastaut syndrome; *N*-CLB = *N*-desmethylclobazam; PBO = placebo; PopPK = population pharmacokinetics; STP = stiripentol; VPA = valproic acid.
[a] STP or PBO was added to a regimen of CLB and VPA. Mean (STICLO-France) or median (STICLO-Italy) dosage of CLB was 0.5 mg/kg/day; mean or median dosage of VPA ranged from 20.7 to 27.7 mg/kg/day.
[b] Virtual subjects simulated using PopPK modeling of data from CONTAIN.
[c] Median C_{min}.

successfully manage treatment-refractory seizures in patients with LGS and Dravet syndrome [2,3]. Thus, it is likely that a substantial proportion of patients in these populations will be concomitantly treated with CLB and CBD, as was the case in the pivotal CBD studies [6–8]. Some patients may also receive concomitant CLB and STP. In the present analysis, we expand upon previous studies detailing the PK interactions between CLB and CBD [15–17] or STP [21] by using modeling to examine the PD interactions between these drugs.

Population PK/PD modeling of predicted exposures to both CLB and *N*-CLB indicated that CLB dosages of 1.0 to 2.0 mg/kg/day could be clinically beneficial to patients with refractory seizures. We also modeled the contributions of CLB, *N*-CLB, and age to somnolence in the phase 3 CONTAIN trial. Somnolence was correlated with increased age and *N*-CLB concentration, but not with CLB concentration. Age and *N*-CLB concentration accounted for 66% of the probability of a patient experiencing sedation-related AEs. Somnolence is also a reported AE of CBD [5]. Coadministration of CBD and other AEMs, including CLB, may further increase the likelihood of somnolence. Several other commonly coadministered AEMs have somnolence as a adverse effects, including valproic acid, lamotrigine, and levetiracetam [33–35]. Therefore, these medications may have also contributed to the probability that a patient will experience somnolence.

In an open-label clinical trial of CBD in patients with treatment-resistant epilepsy, half of patients concomitantly taking CLB experienced somnolence, whereas only one-fifth of patients taking CBD, but not CLB, experienced somnolence, suggesting an additive effect on somnolence when CBD and CLB are coadministered [5]. Similar rates of somnolence among patients taking CBD and CLB (45%) compared with patients taking CBD, but not CLB (19%), were observed in a study of CBD in patients with Dravet syndrome [6]. The present analysis suggests that *N*-CLB levels but not CLB levels were associated with somnolence.

Treatment with CBD increases plasma levels of the active CLB metabolite, *N*-CLB [15–17]. Previous work demonstrated a 3-fold elevation of the mean (C_{max} [peak plasma level]) and exposure of *N*-CLB when CBD was coadministered with CLB, likely due to inhibition of CYP2C19 by CBD [4,12]. These results are similar to recent PK findings. A study examining DDIs between CBD and CLB, STP, or valproate in healthy adult volunteers found that individuals exposed to both CBD and CLB had a 3.4-fold increase in the C_{max} of *N*-CLB; this increased exposure was observed in all 13 participants [17]. A previous study in patients with Dravet syndrome also found increases in mean *N*-CLB concentrations (≥166%) in patients taking CLB and CBD concomitantly [16]. It has been suggested that the CLB dosage may need to be adjusted when CBD is used as adjunctive therapy [4,9]. However, there are currently no published PK or PD studies that directly examine the exposure–response relationship of the medications alone and in combination. Specifically, there are no data to suggest that preemptive dose reduction of CLB is necessary when initiating concomitant CBD; rather, dose reduction may be considered if CLB-related AEs occur [4]. The estimated mean half-life of *N*-CLB (range: 71–82 h) is approximately twice as long as that of CLB (range: 36–42 h) [1]. Because CLB levels decrease more rapidly than *N*-CLB levels, the therapeutic effects of CLB may decrease more quickly than any adverse effects associated with *N*-CLB exposure during dose reduction. One could speculate that if there is a gap in treatment between the reduction of CLB dose and achievement of therapeutic levels of CBD (e.g., a delay to add-on CBD while levels of *N*-CLB normalize), there could be an increased risk of breakthrough seizures. Reduction of *N*-CLB levels may be further slowed by the inhibition of CYP2C19 by CBD [12]. Furthermore, it is also possible that the increased blood levels of *N*-CLB that occur when CBD is added to CLB may result not only in increased adverse effects such as somnolence but also in increased efficacy in seizure control [16,18]. An open-label CBD trial in patients with treatment-resistant epilepsy found in a post hoc analysis that 51% of patients taking both CBD and CLB experienced a 50% or greater reduction in seizures, whereas only 27% of patients not taking CLB experienced this magnitude of seizure reduction [5].

Thus, coadministration of CLB and CBD may enhance both the therapeutic effect and the occurrence of AEs of *N*-CLB, suggesting the need for therapeutic drug monitoring of plasma levels of both CLB and *N*-CLB when used concomitantly with CBD [16,18]. However, because of the lack of a verified therapeutic window for *N*-CLB, decisions to lower doses of CLB may be best made based on clinical response rather than blood levels.

Treatment responder rates in the STICLO studies were significantly higher in the STP and CLB groups compared with the placebo and CLB groups; however, patients receiving placebo and CLB were also receiving suboptimal CLB dosages (approximately 0.5 mg/kg/day) [19]. Patients receiving STP and CLB had similar treatment response rates to PopPK-modeled doses of CLB. Because of the suboptimal CLB doses in the STICLO studies, the therapeutic benefit of STP for seizure reduction may have been overestimated. Notably, coadministration of STP and CLB increased plasma levels of *N*-CLB [19].

The separate analyses of the individual effects of CBD and STP on CLB/*N*-CLB levels can provide some insight into the DDIs these drugs may share. However, a direct comparison between CBD and STP and their effects on CLB and *N*-CLB has not yet been published to our knowledge. A study of healthy control subjects examined coadministration of CBD and CLB as well as coadministration of CBD and STP [17]. Although CBD and CLB coadministration resulted in an increase in the active metabolites of both drugs (i.e., *N*-CLB for CLB and 7-hydroxycannabidiol for CBD), CBD and STP coadministration did not exhibit any clinically meaningful DDIs; a parallel analysis of CLB and STP was not performed in this investigation [17]. Further work directly comparing DDIs between CLB and CBD and STP is warranted.

Some patients with epilepsy have polymorphisms in the gene coding for CYP2C19 that can affect *N*-CLB metabolism and plasma

Table 2
Summary of predictors of somnolence in the CONTAIN clinical trial using penalized logistic regression.

Variable	Coefficient	SE	OR	Lower 95% CI OR	Upper 95% CI OR	*P* value
Intercept	−1.52	0.275				
N-CLB	0.187	0.0716	1.21	1.06	1.40	0.00470
Age	0.0403	0.0154	1.04	1.01	1.07	0.00736

CI = confidence interval; *N*-CLB = *N*-desmethylclobazam; OR = odds ratio; SE = standard error.

concentrations [36,37]. Because CBD- and STP-mediated inhibition of CYP2C19 plays a role in elevating *N*-CLB levels in patients receiving CLB [10,12,38], it is possible that patients with these CYP2C19 polymorphisms may experience DDIs when receiving both CLB and CBD. Furthermore, there may be differences in the risk of DDIs between CYP2C19 poor metabolizers and CYP2C19 extensive metabolizers. Interestingly, there are data suggesting that the impact of STP enzyme inhibition may be less in CYP2C19 poor metabolizers [39]. It is unknown, however, whether coadministration of CBD to a patient who is a CYP2C19 poor metabolizer would result in PK/PD relationships similar to those found in this analysis.

Although PopPK/PD analysis is a well-established method of modeling DDIs and other drug properties when clinical data are relatively sparse [40], this analysis could have been improved with the addition of larger sample sizes in both the CBD and STP groups. It can be impractical to design a study to collect this kind of PK data from patients, particularly in pediatric patients. In this analysis, we have made optimal use of available data by comparing it with model-generated PopPK data to provide critical, potentially clinically relevant information to clinicians. However, further work is needed before specific clinical recommendations can be made when CLB and CBD are coadministered. Future work can build on this PopPK/PD analysis to further characterize potential DDIs and optimize efficacy and patient safety.

4.1. Clinical considerations

Although more work is needed to fully characterize DDIs between CLB and CBD or STP, a few general clinical recommendations can be made. Treatment of pharmacoresistant seizures in patients with LGS or Dravet syndrome can be challenging. We now have clinical evidence that novel AEMs such as STP and CBD can provide additional options for patients, particularly when added to established AEMs such as CLB. When a patient treated with CLB initiates concomitant treatment with CBD or STP, AEs may occur. Before initiating one of these AEMs in patients currently receiving CLB therapy, obtaining baseline CLB and *N*-CLB plasma concentrations as benchmarks for each patient is good clinical practice. After the initiation of CLB therapy, clinicians should closely monitor patients for AEs such as somnolence. If AEs do occur, appropriate dose reductions may be considered. Because *N*-CLB levels vary among individuals and there is no verified therapeutic window for CLB or *N*-CLB, plasma drug level monitoring decisions should be made on an individual basis, and changes in the doses of CLB, CBD, or STP should be based on a patient's clinical response and not on exposure levels. When the patient demonstrates seizure reduction accompanied by an intolerable AE, there are 3 possible therapeutic interventions: (1) dose reduction of CLB, (2) dose reduction or discontinuation of CBD or STP, or (3) dose reduction or discontinuation of CBD or STP, accompanied by a dose increase of CLB.

Because there is currently no evidence-based consensus on how to treat patients who require administration of multiple AEMs to manage seizure disorders, it is difficult to make more detailed clinical recommendations regarding dosing, monitoring plasma levels, and testing for CYP2C19 polymorphisms. The current work describing the PK and PD effects of combining CLB and CBD or STP is intended to provide data to help establish the framework for future studies examining the clinical consequences of these DDIs.

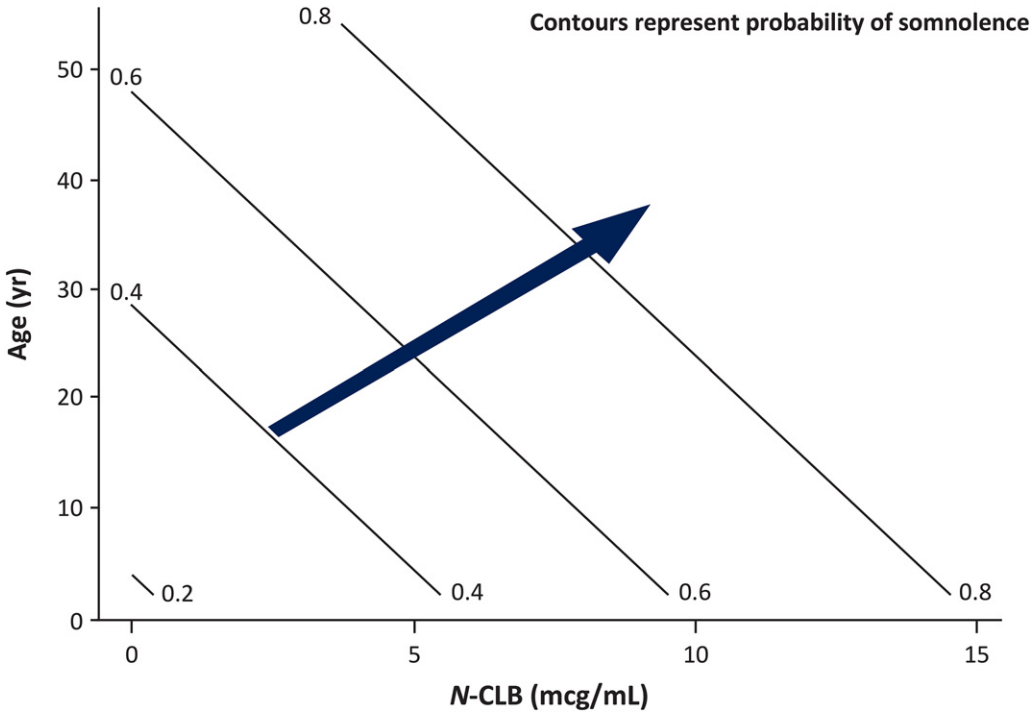


Fig. 4. Effect of age and *N*-CLB concentration on somnolence. *N*-CLB = *N*-desmethylclobazam.

5. Conclusions

An increase in *N*-CLB plasma concentration is likely to occur when either CBD or STP is added to CLB, which could increase desired treatment effects or potentially increase the likelihood of AEs such as somnolence, necessitating dose modification. Greater awareness of both the PD and PK consequences of the DDIs between CLB, CBD, and STP is critically important for optimization of treatment efficacy and safety.

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Declaration of competing interest

P. Klein has served as a consultant for Alliance, Eisai, Engage Pharmaceuticals, Lundbeck, Sunovion, and UCB Pharma; has served as a speaker for Eisai, Sunovion, and UCB Pharma; and has received research support from Eisai and Lundbeck. D. Tolbert is an employee of Lundbeck. B. E. Gidal has served as a consultant and speaker for Eisai, Sunovion, UCB, and Lundbeck and has served as a consultant for Upsher-Smith and Greenwich.

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