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A Systematic Review of Population Pharmacokinetics of Carbamazepine

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ABSTRACT

Carbamazepine is a narrow therapeutic index drug requiring therapeutic drug monitoring, while population pharmacokinetics is an approach that can aid individualized dosing regimens and to date, several population pharmacokinetic studies of carbamazepine have been conducted. This systematic review aims to summarize the factors influencing carbamazepine pharmacokinetics and model methodologies, and to identify any knowledge gaps, which may then be used to inform future studies. PubMed and Scopus databases were systematically searched from the date of their inceptions to August 2019. All population pharmacokinetic studies of carbamazepine performed in humans using a nonlinear mixed-effect modeling approach were extracted from these databases and included in this review. Twenty-three articles were included. A one-compartment pharmacokinetic model was employed in most of these studies. While body size, carbamazepine dose, co-medications, age, gender, race, and CYP1A2 polymorphism were identified as significant predictors of carbamazepine clearance, weight was the only significant predictor of the volume of carbamazepine distribution. Exponential and additive relationships were the most frequently used models when analyzing respectively inter-individual and residual variability, and the magnitude of inter-individual variability on carbamazepine clearance ranged from 1.5% to 44.5%. Seventeen of the studies contained a model evaluation, and of these, an external evaluation was conducted in ten. This review highlights the significant predictors of carbamazepine pharmacokinetics that have been identified. However, since information regarding the relationship between carbamazepine pharmacokinetic variability and its pharmacodynamics is lacking, future research relevant to this issue may be required.

Keywords: Carbamazepine, nonlinear mixed-effect modeling, population pharmacokinetics, systematic review

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INTRODUCTION

Carbamazepine (CBZ) is a first-generation antiepileptic drug commonly prescribed for the treatment of partial, generalized tonic-clonic (grand mal) and mixed seizures [1]. CBZ exerts its mechanism of action by blocking voltage-dependent sodium channels [2], and studies indicate that CBZ also acts as a calcium antagonist and glutamate release inhibitor [2].

Because of its lipophilicity, CBZ is absorbed slowly, with peak concentrations following immediate-release formulation administration of 6 hours (with a range of 2 to 8 hours) [3]. The rate of CBZ absorption is variable, and consumption of a high-fat diet increases the rate but not the extent of absorption [4, 5].

Plasma protein binding of CBZ is relatively high, with a free fraction of 0.2-0.3 [6, 4, 7], and assuming complete bioavailability, CBZ's calculated apparent volume of distribution (V_d) is approximately 1 L/kg. With less than 2% excreted unchanged via the kidneys [4], the drug is almost entirely metabolized by the liver, and of this, approximately 65% is metabolized by oxidation and, to a lesser extent, hydroxylation [5]. The major active metabolite of CBZ metabolized via oxidation is CBZ-10,11-epoxide (CBZ-E) [5, 4] and this is then subsequently hydrolyzed to CBZ-diol and excreted in the urine [3]. Cytochrome P450 (CYP) 3A4, and CYP2C8 [8, 3] are the enzymes responsible for the production of CBZ-E, while CYP1A2 is the enzyme responsible for its aromatic hydroxylation [8]. The drug is also known to induce its own metabolism (autoinduction) [6, 4], and the time to a steady-state of CBZ is highly variable, ranging from 4 to 30 days depending on the onset and the extent of autoinduction [4].

CBZ has a reported half-life of 35.9 and 20.9 hours following respectively a single dose and multiple dose administration [9], and the reported CBZ clearance (CL_{CBZ}) at steady-state in adults and children are 50-100 mL/h/kg and 50-200 mL/h/kg [6]. In addition to its autoinductive property, CBZ is also a potent CYP inducer, thus indicating its potential to precipitate drug interactions [3].

CBZ is a narrow therapeutic index drug with high pharmacokinetic variability, and its disposition may be influenced by factors including age, weight, concomitant medications [10], and genetic polymorphisms [11], which may then complicate drug therapy. Evidence also indicates that CBZ therapy may be improved with the aid of therapeutic drug monitoring (TDM) and in this direction, a recent approach used to guide drug dosing has been to incorporate a population pharmacokinetic (PopPK) model with Bayesian estimation techniques, and to date, several CBZ PopPK models have been developed. Given that CBZ use is ongoing, information relevant to CBZ

pharmacokinetic variability is crucial in supporting CBZ-based therapies.

METHODS

Literature search

A systematic search for CBZ PopPKs was conducted using the PubMed and Scopus databases. The search range ran from the date of inception of these databases to August 2019 and employed the following criteria: ((“carbamazepine” [MeSH Terms] OR “carbamazepine” [All Fields]) AND (“population pharmacokinetic’ OR “pharmacokinetic model” OR “nonlinear mixed effect*” OR “NONMEM”)). Reference lists of all retrieved articles were then reviewed for any links to additional studies. The inclusion criteria for this review were that: 1) the studies were conducted on humans; 2) CBZ was prescribed as the treatment drug; and 3) the studies used a PopPK analysis that employed a nonlinear-mixed effect modeling approach. Studies were excluded if they were: 1) not written in English; 2) reviews, methodologically-oriented, expert opinions or case reports; 3) *in vitro* or animal studies; or 4) based on methods other than nonlinear mixed effect modeling.

Data extraction

The following information was extracted from the studies: 1) The characteristics of the study (e.g. study design, sampling time, number of samples, assay methods, etc.); 2) the participants’ characteristics (e.g. age, body size, co-administered drugs, and comorbidities); and 3) the PopPK analysis (e.g. structural, statistical, and covariate models, as well as evaluation approach).

Blood samples were classified into either sparse sampling, when trough concentrations with or without additional levels were obtained, and extensive samplings, when six or more CBZ concentrations were available. Model evaluations were then categorized into basic internal, advanced internal, and external approaches [12].

Simulations using selected population pharmacokinetic models

To support the clinical application of the proposed PopPK models, five models that were developed using a one-compartment structure and performed an external model evaluation, were chosen for the simulations. These criteria were specified to ensure the external predictability of the chosen models and to imitate real-world clinical situations, where typically only trough concentrations are obtained. One thousand simulations were performed for each PopPK model to compare the steady-state trough concentrations of CBZ using dosing regimens of 500 mg bid, 600 mg bid, and 800 mg bid. The final parameter estimates, model structure, and significant covariates, together with the magnitude of inter-individual and residual variability of the selected models were used for the simulations.

RESULTS

Study identification and study design

A PRISMA flow diagram of the study identification and selection process is presented in Figure 1. A total of 257 non-redundant studies were screened for this review, leaving 41 articles for further assessment. Of these, 19 were removed in line with the exclusion criteria described above, leaving 23 articles to be included in this review.

Of the 23 PopPK studies identified, two [13, 14] utilized simulated datasets, ten [15-24] collected data retrospectively, and eleven [25-35] were conducted prospectively. The sample sizes ranged from 13 to 585 subjects and the majority were conducted using epileptic patients, with the exception of one study [15] that incorporated psychiatric patients and one other [19] that utilized data from both epileptic patients and healthy volunteers. Thirteen studies [15, 25, 16, 17, 26, 27, 21, 22, 31, 32, 23, 24, 35] were single-center, and seven [18-20, 28-30, 33] were multicenter. The characteristics of the study population are summarized in Table 1.

Dosing regimens and drug sampling

Most of these studies used data based on the oral administration of CBZ and only two studies employed data derived from intravenous infusion [30, 33], although a further two analyzed data following both oral and intravenous administration of CBZ [34, 35]. Nineteen studies employed sparse sampling strategies [15-17, 26, 18, 20, 27-29, 21, 22, 31, 32, 23, 13, 24, 34, 35, 14], three used extensive sampling strategies [25, 30, 33] and one study utilized both extensive and sparse sampling datasets [19]. Table 2 summarizes the dosing regimens, sampling strategies, and analytical methods used to determine CBZ levels and/or its metabolites.

Population pharmacokinetic models of carbamazepine

CBZ pharmacokinetics was described using a one-compartment model in nineteen studies [15, 25, 17, 26, 18, 19, 27-29, 14, 21, 22, 30, 32, 35, 31, 23, 24, 34], while one used a two-compartment model [33] and two more used a steady-state model [20, 16]. One further study employed a mixture model to analyze CBZ hypometabolizers [18]. With regard to the studies that used a one-compartment model structure, population estimates of the V_d for a 70 kg-person ranged from 25.9 to 138 L, whereas with the two-compartment model, estimates of central and peripheral V_d for a 70 kg-patient were 142 L and 175 L, respectively. The rate of CBZ elimination was described as a first-order process in all studies.

Most studies (>50%) tested the effects of body size, age, gender, CBZ dose and concomitant medications on CL_{CBZ}. Five studies [15, 20, 32, 24, 33] tested the impacts of ethnicity and smoking status on CBZ pharmacokinetics, and the influence of alcohol consumption and formulations were assessed in respectively four [15, 18, 32, 33] and five [25, 20, 28, 29, 21] studies. Only two studies evaluated the impact of *CYP450* (*CYP1A2* and *CYP2C8*) genotypes on CL_{CBZ} [34, 35]. The impact of laboratory values on CBZ pharmacokinetics were assessed in a further three studies [32, 24, 33]. A summary of tested and retained covariates is presented in Table 3.

Body size [15, 25, 16-18, 26, 19, 20, 28, 29, 33, 21, 31, 24, 34, 35] and CBZ dose [16, 17, 19, 28, 29, 14, 21, 31, 24, 35, 34] were found to be significant predictors of CL_{CBZ} in most studies. Ten studies identified significant effects of co-medications on CL_{CBZ} [16, 17, 26, 18, 20, 28, 29, 21, 22, 31, 32] and six did so with regard to age [17, 18, 20, 29, 22, 31]. In these studies, medications that were taken concurrently and that had a significant impact on CL_{CBZ} included valproic acid, phenobarbital, phenytoin, and felbamate, while the impact of gender [24, 34, 35] and race [33] were also reported. Beyond this, CYP1A2 polymorphism was found to be a significant predictor of CL_{CBZ} [34], although with regard to the volume of distribution, weight was found to be the only significant predictor [19, 29, 32, 33].

As for inter-individual variability models, the exponential relationship was the most frequently used (52.2%), whereas the additive model (34.8%) was most commonly used to model residual variability. Inter-individual variability of CL_{CBZ} ranged from 1.5% to 44.5%. Table 4 summarizes the covariate-parameter relationships,

magnitudes of inter-individual and residual variability, and population estimates of CBZ pharmacokinetic parameters.

Models were evaluated in seventeen studies (73.9%) (Table 4). Of these, ten (43.5%) employed an external model evaluation, where an external dataset (with sample sizes of between 13 and 74 subjects) was used to compare predicted CBZ concentrations with the final models. Seven studies (30.4%) evaluated the final models using an advanced internal approach, while six (26.1%) did not perform any model evaluations. However, two of these modeled with simulated datasets.

Simulations

The simulated trough CBZ concentrations are presented in Fig. 2, and all five selected pharmacokinetic studies resulted in a relatively similar range of simulated CBZ concentrations. The impacts of concomitant antiepileptic drugs (phenobarbital, phenytoin, and valproic acid) on CBZ levels were also comparable across studies.

DISCUSSION

Based on the included PopPK studies, weight was the only significant predictor of V_d [19, 29, 32, 33], though studies have indicated that physiological factors including age, gender, and body size can affect the proportion of body water, lean body mass, and body fat, which in turn then affect the V_d of the drug [36]. Given that CBZ is lipophilic and that patients with higher weight might have a greater proportion of bodyfat, this would tend to lead to a higher V_d.

Body weight was the most frequently used indicator for CL_{CBZ}, however, the effects of weight on CL_{CBZ} are not entirely clear and there is some conflict in the results. Although most studies reported an increase in CL_{CBZ} with increasing weight, Yukawa *et al* [16] and Chan *et al* [20] reported a nonlinear decrease in CL_{CBZ} with increasing weight, and this might be explained by the organ maturation that is normally achieved at age 14 to 16 years [16, 20]. This would then lead adults to have a lower CBZ metabolism, compared to children, although in addition, the discrepancies between the effects of weight on CL_{CBZ} could be due to differences in patient characteristics.

Five studies reported an increase in CL_{CBZ} with increasing age [17, 18, 20, 29, 22, 31], while one study produced separate models for pediatric and adult populations [31]. Although the estimated CL_{CBZ} for the two populations were not substantially different, it was found that the influence of age on CL_{CBZ} was more pronounced in the pediatric population than among adults. Again, this might be attributable to the maturation of elimination organs in adults.

Concomitant medications significantly influencing CL_{CBZ} included valproic acid [16, 26, 28, 29, 21, 22], phenobarbital [16, 17, 26, 18, 20, 29, 28], phenytoin [26, 18, 29, 28, 32], and felbamate [18] but from earlier pharmacokinetic studies, the influence of valproic acid on CBZ pharmacokinetics is unclear and after co-administration with valproic acid, CBZ concentrations may increase [37, 38], decrease [38, 39], or remain unchanged [40]. These conflicting results have also been reported in PopPK studies, and Gray *et al*. reported that no change in CL_{CBZ} was observed when valproic acid was co-administered [26], while in contrast, other studies showed an increase in CL_{CBZ} in the range of 7% to 21% when valproic acid was added as a concomitant drug [16, 22, 28, 29]. This could be explained by the higher protein binding capacity of valproic acid compared to CBZ, and CBZ bound-plasma protein could then be replaced by valproic acid, resulting in higher free CBZ levels, which would in turn lead to higher CL_{CBZ}.

Phenytoin and phenobarbital are both known to induce production of CYP3A4, which is responsible for the metabolism of CBZ to CBZ-E, resulting in a decrease in CBZ concentrations, and from the PopPK studies, the magnitude of the increase in CL_{CBZ} caused by phenytoin or phenobarbital ranged from 16% to 45%.

As for felbamate, an increase in CL_{CBZ} of 17% was reported, although felbamate exhibits both inhibitory and inductive effects on oxidative drug metabolism. Also, a classical pharmacokinetic study shows that felbamate increases CL_{CBZ} by 10-42%, which is in agreement with the results of these PopPK studies. When CBZ was administered with both phenytoin and felbamate or phenytoin and phenobarbital, a higher increase in CL_{CBZ} was observed (62%) but this interaction is of limited clinical significance since the therapeutic effect of the added concomitant drugs outweighs the risk of reduced CBZ effects [3].

A positive correlation between CBZ dose and CL_{CBZ} was observed [16, 17, 19, 28, 29, 34, 24, 35, 31, 21], but the effect of CBZ dose on its clearance could be attributed to the TDM effect in that patients with higher clearance tend to receive a higher dose, rather than exhibiting an intrinsically high clearance. Indeed, the TDM effect of CL_{CBZ} was proved by Ahn *et al* using a simulated dataset [14].

Two studies investigated the influence of CYP polymorphisms on CL_{CBZ}. One study reported a non-significant effect of *CYP2C8*3* on CL_{CBZ} [35], while the other demonstrated that the *CYP1A2*-163A/A genotype had a significant influence on CL_{CBZ} [34]. However, the magnitude of this effect is relatively low and patients carrying *CYP1A2*-163A/A genotype will have CL_{CBZ} of 0.019 L/h higher than those carrying *CYP1A2*-163C/C and C/A so a routine *CYP1A2* genotype screening might not be necessary. Nevertheless, this difference should be used as a predictor of CL_{CBZ} when this information is available.

Only one study identified a significant effect of race on unbound CL_{CBZ}, with 30% higher unbound CL_{CBZ} in Caucasians compared to African Americans [33]. This effect could be due to the higher incidence of *CYP3A4*1B* in African Americans, since this variant allele is associated with a reduction in enzymatic activity [33]. This effect is in fact supported by a study reporting an allele frequency of *CYP3A4*1B* in Caucasians as 0.04 and in African Americans as 0.27 [41] and hence, a higher CBZ dose might be needed in this patient population.

Simulations using selected PopPK models showed a similar trend across studies. For CBZ monotherapy, the median simulated trough concentrations following 500 mg bid, 600 mg bid, and 800 mg bid were within the therapeutic range of 4-12 mg/L for all selected studies. However, co-administration with phenobarbital, phenytoin, or valproic acid lowered the median simulated trough concentrations to a level that is close to the therapeutic range's lower limits, and administration of CBZ 500 mg bid or 600 mg bid with more than one antiepileptic drug (e.g. with phenobarbital and phenytoin, or with phenobarbital and valproic acid) resulted in median simulated trough concentrations that were lower than 4 mg/L (Fig. 2). However, the impact of these low CBZ concentrations could be offset by the effects of concomitant antiepileptic drugs, and clinical responses should be taken into consideration before making any dosage adjustments.

Based on this systematic review, although CBZ PopPKs have been extensively studied among different ethnic groups, the relationship between its pharmacokinetic

variability and the pharmacodynamics remains unclear and as a result, predictions of CBZ's therapeutic outcomes are not well established. Thus, the development of a PopPK-PD model for CBZ might be undertaken to fill the gap in our knowledge regarding CBZ's clinical applications.

CONCLUSION

This review highlights the significant factors influencing CBZ pharmacokinetics. The most frequently identified covariates are weight, age, CBZ dose, and concomitant medication with other antiepileptic drugs. The selection of a PopPK model for use in personalizing dosage regimens during CBZ therapy should be based on the characteristics of the target population, as well as on the predictive ability of the models with regard to the target population. However, none of the included studies explored the relationship between PopPK of CBZ and PD, and future research on CBZ therapy could focus on the link between PK-PD models, which would then allow for the better characterization of therapeutic outcomes.

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CONFLICT OF INTEREST

The authors have no conflicts of interest that are relevant to the content of this article.

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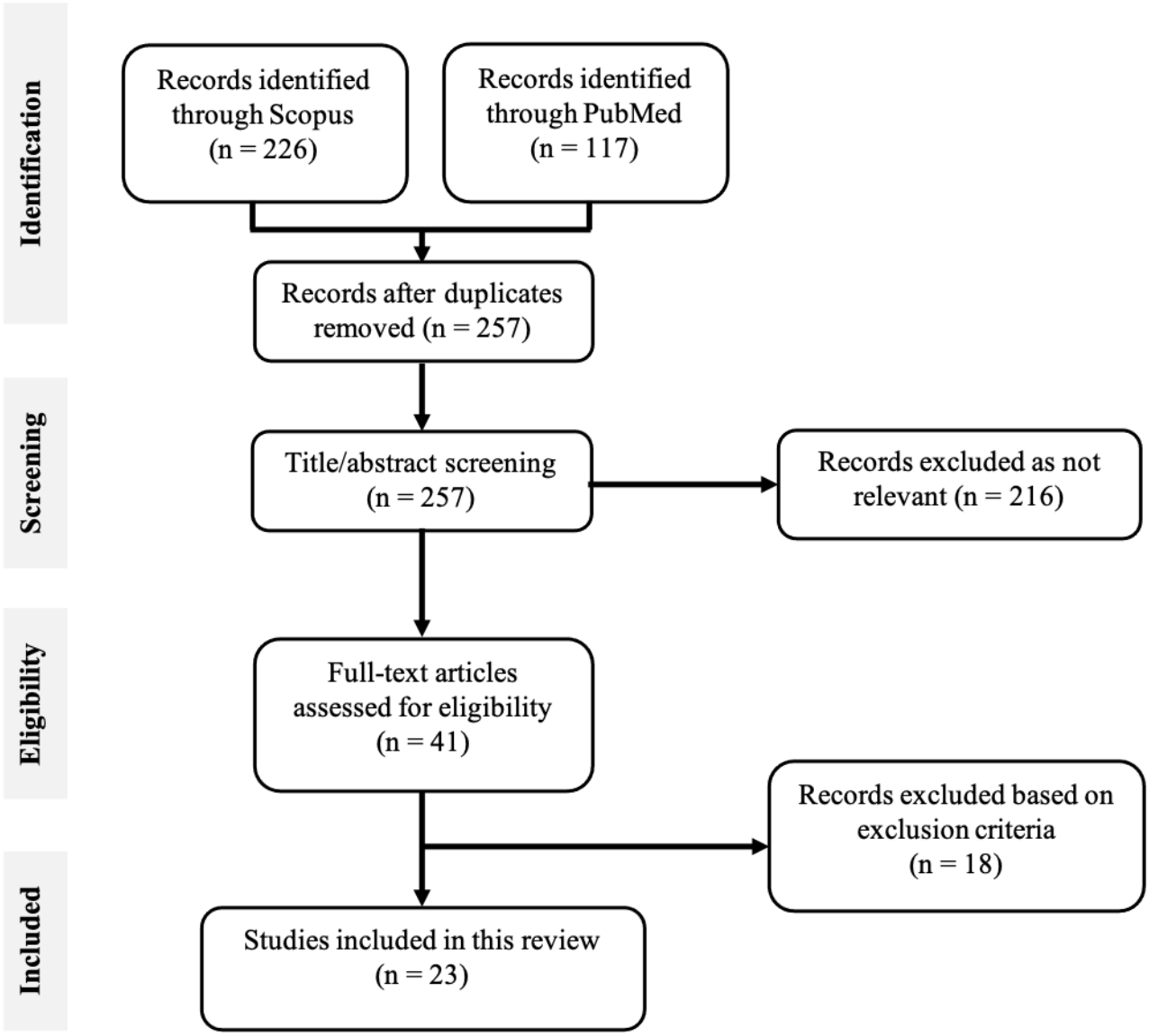

Fig. 1. PRISMA flow diagram of the study identification

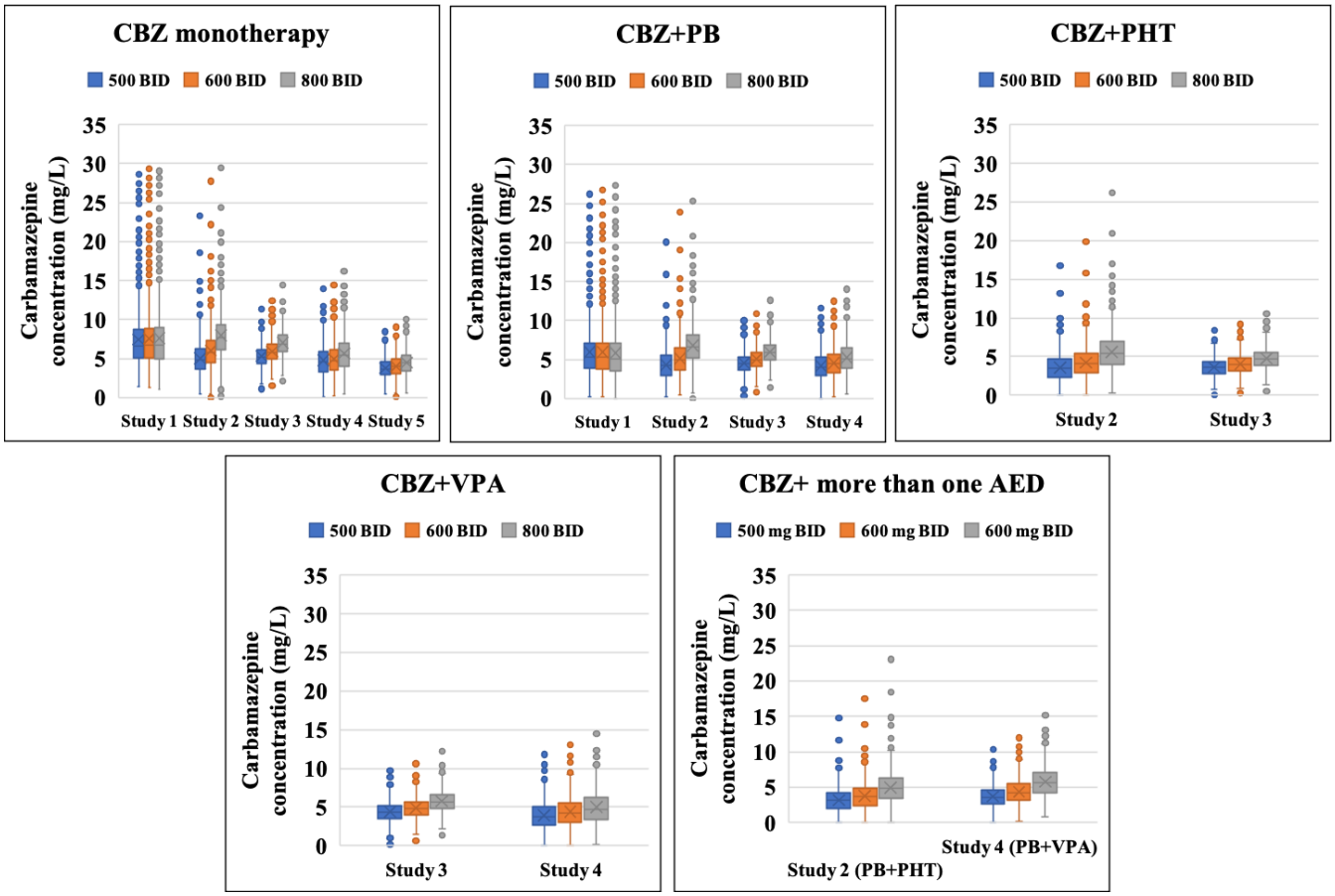

Figure 2. Simulated carbamazepine concentration using the selected population pharmacokinetic models. Study 1, 2, 3, 4, and 5 are simulations using the models of Iribanegaray D *et al.* (17), Graves NM *et al.* (18), Jiao Z *et al.* (29), Vucicevic K *et al.* (21), and Kong ST *et al.* (24), respectively.

Table 1. Characteristics of patient population

No	Study	Study design	Country	Center	Sample Size	Male	Female	Mean age (years) [range]	Mean weight (kg) [range]	Patient characteristics	Smoking (%)	Alcohol use (%)	Co-medication causing drug interaction
1	Martin ES *et al.* [15]	Retrospective	USA	Single	45	71	29	40 [19-69]	73 [46-99]	Epilepsy, psychiatry	Yes (73.3%)	Yes (33.3%)	Antipsychotic, PB, PMD, PHT, VPA
2	Miller R *et al.* [25]	Prospective, open, crossover trial	South Africa	Single	13	61.5	38.5	25.4 [18-40]	72.9 [54-91]	Epilepsy	No	No	No (monotherapy)
3	Yukawa E *et al.* [16]	Retrospective	Japan	Single	466	49	51	15 ± 9.2 [0.3-72.9]	41.3 ± 17.7 [4.5-90]	Epilepsy	NR	NR	VPA, PB, PMD, CZP
4	Iribanegaray D *et al.* [17]	Retrospective	Spain	Single	201	51.2	48.8	9.5 [1-14]	35 [9 – 78]	Epilepsy	NR	NR	PB, VPA
5	Gray AL *et al.* [26]	Prospective	South Africa	Single	72	67	33	8.7 ± 3.8 [2.3-16.3]	29.5±13.7 [9-30]	Epilepsy	NR	NR	VPA (26%), PB (8%), PHT (10%), PB+PHT (1%)
6	Graves NM *et al.* [18]	Retrospective	USA	Multi	829	49	51	35 [17-89] (age ≥ 70 years = 1.7%)	75 [28-159]	Epilepsy	Yes (28%)	Yes (22%)	PHT (26%), VPA (19%), PB (15%), FBM (6%)
7	Reith DM *et al.* [19]	Retrospective (2 datasets: bioequivalence (BE) study and TDM study	Australia	Multi	91 BE: 18 TDM: 73	82.7	17.3	18.1 [0.7-37.2] BE study: 23.3 [18-35] TDM data: 10.9 [2-37]	63.6 [9.8-106]	Healthy volunteers, Epilepsy	NR	NR	VPA (10%), LTG (2.7%), PHT (1.2%), PB (1.4%)
8	Chan E *et al.* [20]	Retrospective	Singapore	Multi	193	52.6	47.4	12.5 ± 10.1 [0.3-51]	34.9 ± 20.5 [4.8-84.5]	Epilepsy	NR	NR	Monotherapy (52.3%), PHT (12.2%), PB (26.5%), PHT+PB (2.3%)
9	Deleu D *et al.* [27]	Prospective	Oman	Single	48	43.7	56.3	27.8 ± 13.0 [18-72]	60.8 ± 14.4 [35-120]	Epilepsy	NR	NR	No (monotherapy)
10	Jiao Z *et al.* [29]	Prospective	China	Multi	585	63.4	36.6	23.3 [1.2-85.1] (Age > 65 = 15)	53 [5-115]	Epilepsy	NR	NR	VPA, PHT, PB, VPA+PB, VPA+PHT, PHT+PB
11	Jiao Z *et al.* [28]	Prospective	China	Multi	408	60.0	40.0	22.6 ± 14.9 [1.3-85.1]	52.4 ± 18.1 [5.0-101.0]	Epilepsy	NR	NR	VPA, PHT, PB, VPA+PB

No	Study	Study design	Country	Center	Sample Size	Male	Female	Mean age (years) [range]	Mean weight (kg) [range]	Patient characteristics	Smoking (%)	Alcohol use (%)	Co-medication causing drug interaction
12	Ahn JE *et al*. [14]	Simulation dataset	USA	NR	100 (2 datasets: pre TDM and post TDM)	NR	NR	NR	Simulated from a log normal with a mean of 70 kg and CV of 20%	NR	NR (simulat-ed conc.)	NR (simulat-ed conc.)	NR
13	Vucicevic K *et al*. [21]	Retrospective	Serbia	Single	265	51	49	37 ± 16	71 ± 16	Epilepsy	Yes (20%)	NR	PB, VPA, LTG, BZD
14	Jankovic SM *et al*. [22]	Retrospective	Serbia	Single	97	45.4	54.6	14.7 ± 11.4 [2-67]	45.6 ± 20.9 [13-115]	Epilepsy	NR	NR	Monotherapy or polytherapy with VPA
15	Punyawudho B *et al*. [30]	Prospective	USA	Multi	15	60	40	39	78	Epilepsy	NR	NR	No (monotherapy)
16	Milovanovic JR *et al*. [31]	Prospective	Serbia	single	Ped: 98 Adult: 53	Ped: 67.4 Adult: 43.4	Ped: 32.6 Adult: 56.6	Ped: 8 ± 3 [1-14] Adult: 32 ± 15 [15-65]	Ped: 31 ± 18 [8-95] Adult: 67 ± 13 [37-98]	Epilepsy	NR	NR	VPA, LTG, TPM, PB
17	Punyawudho B *et al*. [32]	Prospective	USA	Single	121	97.5	2.5	70.5 [60-96]	81.4 [50-129]	Epilepsy	Yes (25.6%)	Yes (29.8%)	PHT (16.5%), PB (0.8%), VPA (1.7%)
18	EL Desoky ES *et al*. [23]	Retrospective	Egypt	Single	302 (Pediatric: 118, adult: 184)	55.6	44.4	22.1 ± 12.4	55.3 ± 19.7	Epilepsy	NR	NR	PHT, VPA, LTG, CZP
19	Ding J *et al* [13]	Simulation dataset	Chinese	NR (simulation)	5,000 virtual patients	NR	NR	NR	60	Epilepsy (assumed scenario)	NR	NR	Monotherapy
20	Kong ST *et al*. [24]	Retrospective cohort (cross-sectional)	Singapore	Single	71	46.5	53.5	42.7 ± 11.2 [22.3-77.8]	65.7 ± 19.0 [39.5-107.4]	Epilepsy	NR	NR	VPA, PB, CLO, LEV
21	Ahmed GF *et al*. [33]	Prospective	USA	Multi	113	53.1	46.9	46.1 ± 14.9 [19-87]	80.6 ± 19.4	Epilepsy	Yes 22/47/44 (smoker/nonsm-oker/ missing)	Yes 24/42/47 (consumer/non-consumer/ missing)	Monotherapy or taking non-interacting medications

No	Study	Study design	Country	Center	Sample Size	Male	Female	Mean age (years) [range]	Mean weight (kg) [range]	Patient characteristics	Smoking (%)	Alcohol use (%)	Co-medication causing drug interaction
22	Djordjevic N *et al.* [34]	Prospective	Serbia	Single	40	60	40	Median = 11 [4-16]	Median = 39 [17-65]	Epilepsy	NR	NR	Monotherapy (90%), VPA (10%)
23	Milovanovic DD *et al.* [35]	Prospective	Serbia	Single	40	60	40	Median = 11 [4-16]	median = 39 [17-65]	Epilepsy	NR	NR	Monotherapy (90%), VPA (10%)

BE: bioequivalence, BZD: benzodiazepine, CLO: clobazam, CZP: clonazepam, FBM: felbamate, IV: intravenous, LEV: levetiracetam, LTG: lamotrigine, NR: not report, PB: phenobarbital, PHT: phenytoin, PMD: primidone, TDM: therapeutic drug monitoring, TPM: topiramate, VPA: valproic acid

Table 2. A summary of carbamazepine dosing regimens, sampling strategy, and assay methods of the included population pharmacokinetic studies

No	Study	Formul-ation	Route	Mean CBZ Concentration [range]	CBZ dose/day [range]	Frequency	Sampling strategy	Sampling time	Samples/ patient	Total samples	Assay	%CV	LLOQ
1	Martin ES *et al.* [15]	IR	Oral	7.7 mg/L [2.6-14.5 mg/L]	1000 mg/d [300-1800 mg/d]	NR	Sparse	Trough concentration	1-11 (mean 35)	159	Enzyme mediated immunoassay.	NR	NR
2	Miller R *et al.* [25]	IR and CR (cross over study)	Oral	C_{min} IR: 6.2 mg/L [4.5-9.0 mg/L] CR: 6.7 mg/L [5.1-8.4 mg/L] C_{max} IR: 8.9 mg/L [6.7-11.4 mg/L] CR: 8.7 mg/L [6.3-10.9 mg/L]	707.7 mg/d [400-1000 mg/d]	IR: 3 times/day CR: 2 times/day	Extensive	0,1,2,3,3.5,4,4.5, 5.5,6,6.5,7,7.5,8, 8.5,9,10,11, and 12 h post dose	19 (for each dosage form)	494	HPLC	< 10%	NR
3	Yukawa E *et al.* [16]	IR (tablet or granules)	Oral	C_{ss}: 6.1 ± 1.9 mg/L [1.6 -14.2 mg/L]	9.1 ± 3.6 mg/kg/d [1.5-26.5 mg/kg/d]	2-3 times/day	Sparse	2-6 hours after morning dose	2.17 (calculated)	1010	FPIA	<10%	NR
4	Iribanegaray D *et al.* [17]	IR	Oral	6.3 mg/L [1.6-12.8 mg/L]	14.4 mg/kg/d [2.4-35.3 mg/kg/d]	NR	Sparse	Trough concentration	1.9 (range 1-11)	387	FPIA	<10%	NR
5	Gray AL *et al.* [26]	Suspe-nsion, IR, CR	Oral	NR	NR	NR	Sparse	within 6 h (56%) and 7-23 h after dosing	1 (51 patients), 2-7 (21 patients)	118	EMIT or FPIA	NR	NR
6	Graves NM *et al.* [18]	NR	Oral	7.2 mg/L [1-17.4 mg/L]	964 mg/d [100-3200 mg/d]	1-4 times/day	Sparse	NR	2.2 (calculated)	1834	FPIA, EMIT	NR	NR

No	Study	Formul-ation	Route	Mean CBZ Concentration [range]	CBZ dose/day [range]	Frequency	Sampling strategy	Sampling time	Samples/ patient	Total samples	Assay	%CV	LLOQ
7	Reith DM *et al.* [19]	NR	Oral	6.6 mg/L [1.1-16 mg/L]	12.8 mg/kg [2.63-63.4 mg/kg]	NR	Combined (sparse from TDM study, extensive from BE study)	TDM: < 2 h, 2-4 h, 4-6 h, 6-8 h, ≥ 8 h post dose BE: rich data	4 (1-40)	946 BE: 591 TDM: 355	FPIA (TDM study), HPLC (BE study)	<10%	0.1 mg/L
8	Chan E *et al.* [20]	Syrup (62.3 %), IR tablet (37.7%)	Oral	7.8 mg/L [1-20.5 mg/L]	16.7 mg/kg/d [4.2-66.7 mg/kg/d]	2-4 times/day	Sparse	Trough concentration	1.6 (calculated)	302	NR	NR	NR
9	Deleu D *et al.* [27]	IR tablet	Oral	Free conc.: 1.6 ± 0.4 mg/L [0.7-2.8 mg/L]	9.7 ± 4.4 mg/kg/d [3.1-25.0 mg/kg/d]	NR	Sparse	Trough concentration, 1-6 h following morning dose	2-5	NR	FPIA	<5%	0.047 mg/L
10	Jiao Z *et al.* [29]	IR tablet	Oral	5.40 mg/L [1.1-14.6 mg/L]	9.9 mg/kg/d [1.2-80 mg/kg/d]	2-4 times/day	Sparse	Trough concentration	1.2 (calculated)	687	FPIA	<10%	1 mg/L
11	Jiao Z *et al.* [28]	IR tablet	Oral	5.2±1.9 mg/L [1.0-12.5 mg/L]	9.7 ± 5.7 mg/kg/d [1.7-38.1 mg/kg/d]	NR	Sparse	Trough concentration	1.1 (calculated)	459	HPLC	<8%	NR
12	Ahn JE *et al.* [14]	NA	Oral	NR	1000 mg/d	3 times/day	Sparse	Post dose interval (10-12 pm, 12-14 pm, 14-16 pm)	3 simulated conc.	300	NA (simulated conc.)	NA (simulated conc.)	NA (simula-ted conc.)
13	Vucicevic K *et al.* [21]	IR and CR	Oral	6.4 ± 3.4 mg/L	842 ± 415 mg/d	2-4 times/day	Sparse	Trough concentration and 5 h after morning dose	1-2	423	Homogeno-us enzyme immunoass ay	< 10%	0.5 mg/L (conc. below LLOQ was replace-d with LOQ/2)
14	Jankovic SM *et al.* [22]	IR tablet or syrup	Oral	5.4 ± 1.7 mg/L [0.54-10.10 mg/L]	556.0 ± 238.4 mg/d [100-1200 mg/d]	2-3 times/day	Sparse	Trough concentration or peak concentration	1.1 (calculated)	107	HPLC	< 5%	NR

No	Study	Formul -ation	Route	Mean CBZ Concentration [range]	CBZ dose/day [range]	Frequency	Sampling strategy	Sampling time	Samples/ patient	Total samples	Assay	%CV	LLOQ
15	Punyawudho B *et al.* [30]	IV	10-minute infusion	NR	Infusion of 100 mg dose on 3 occasions (1st: morning after last dose, 2nd: 6-8 days after last dose, 3rd 6-8 week after last dose)	CBZ oral dose was discontinued (this study investigated time course of CBZ de-induction)	Extensive	0, 0.083, 0.25, 0.5, 1, 2, 4, 6, 12, 24, 48,72,96 h after the end of CBZ infusion	13 * 3 occasions	524	LCMS	NR	NR
16	Milovanovic JR *et al.* [31]	IR tablet and syrup, CR	Oral	Pediatric: 6 ± 2 [1-12] Adult: 6 ± 2 [2-10]	Pediatric: 500 ± 223 mg/d [120-1400 mg/d] Adult: 743 ± 315 mg/d [200-1400 mg/d]	1-3 times/day	Sparse	Majority was collected at trough; some was peak conc.	Pediatric: 1.16 (calculated) Adult: 1 (calculated)	Pediatric: 114 Adult: 53	HPLC	< 5%	NR
17	Punyawudho B *et al.* [32]	IR tablet	Oral	NR (all below 20 mg/L)	600 mg/d	NR	Sparse	Convenient sampling	4.6 (calculated)	555	NR	NR	NR
18	EL Desoky ES *et al.* [23]	CR tablet (93.7%), suspension (6.3%)	Oral	NR	15.0 ± 7.84 mg/kg/d [200-1400 mg/d]	NR	Sparse	Trough concentration (11±1.29 h)	1	302	FPIA	<7%	0.5 mg/L
19	Ding J *et al* [13]	NR	Oral	NR	300, 400, 600, 900 mg/d	2-3 times/day	Sparse	Trough concentration	NR	NR	NR	NR	NR
20	Kong ST *et al.* [24]	CR	Oral	8.1 ±2.2 mg/L [2.5-13.8 mg/L]	936.1 ±332.3 mg/d [200-1600 mg/d]	NR	Sparse	Trough concentration	1	72	• Immunoassay (for plasma conc.) • GCMS (for dried blood spot)	•<8% for immunoassay •<15% for GCMS	NR
21	Ahmed GF *et al.* [33]	IV	IV infusion over 10-20 minutes	NR	NR	NR	Extensive	0, 0.083, 0.25, 0.5, 1, 2, 4, 6, 10, 24, 48, 72, 96 h	NR	NR	LCMS	< 5%	0.1 mg/L

No	Study	Formul-ation	Route	Mean CBZ Concentration [range]	CBZ dose/day [range]	Frequency	Sampling strategy	Sampling time	Samples/ patient	Total samples	Assay	%CV	LLOQ
22	Djordjevic N *et al*. [34]	IV (given additional to oral formulations: tablet, syrups)	IV, oral	Before dose adjustment: 6.4±1.6 mg/L [3.5-9.9 mg/L] After dose adjustment: 6.5±1.8 mg/L [2.7-10.6 mg/L]	Before dose adjustment: 15.3±4.4 mg/kg/d [6.9-24.2 mg/kg/d] After dose adjustment: 15.2±4.5 mg/kg/d [6.9-24.2 mg/kg/d]	1-3 times/day	Sparse	Trough concentration (8-12 h after last dose)	2 (at two occasions: at the beginning and 4 weeks after dose adjustment)	NR	HPLC	< 5%	0.5 mg/L
23	Milovanovic DD *et al*. [35]	IV (given additional to oral formulations: tablet, syrups)	IV, oral	For CYP2C8*3 carriers: 0.5 ± 0.2 mg/L For CYP2C8*3 non carriers: 0.4 ± 0.1 mg/L	For CYP2C8*3 carriers: 14.2 ± 5.4 mg/kg (after dose adjustment) For CYP2C8*3 non-carriers: 15.5 ± 4.4 mg/kg (after dose adjustment)	1-3 times/day	Sparse	Trough concentration (8-12 h after last dose)	2 (at two occasions: at the beginning and 4 weeks after dose adjustment)	NR	HPLC	< 5%	0.5 mg/L

BE: bioequivalence, CBZ: carbamazepine, C_{min}: minimum concentration, C_{max}: maximum concentration, C_{ss}, steady-state concentration, CV: coefficient of variation, CR: control-release, EMIT: enzyme multiplied immunoassay, GCMS: gas chromatography mass spectrophotometry, FPIA: Fluorescence polarization immunoassay, HPLC: high performance liquid chromatography, IR: immediate-release, LLOQ: lower limit of quantitation, NR: not report, TDM: therapeutic drug monitoring

Table 3. Tested and retained covariates in population pharmacokinetic models of carbamazepine

No	Study	Tested Covariates												Retained Covariates						
		CBZ dose	Body size	Age	Gender	Race	Co-medication	Smoking	Alcohol use	Dosage forms	Genotype	Laboratory value	Other	CBZ dose	Body size	Age	Gender	Race	Co-medication	Other
1	Martin ES *et al.* [15]	√	√ (WT, IBW, LBW)	X	√	√	√ (antipsychotic, PB, PMD, PHT, VPA)	√	√	X	X	X	X	X	√ (LBW)	X	X	X	X	X
2	Miller R *et al.* [25]	X	√ (WT on CL and V_d)	X	X	X	X	X	X	√ (IR, CR)	X	X	X	X	√ (WT on CL)	X	X	X	X	X
3	Yukawa E *et al.* [16]	√	√ (WT, IBW, LBW)	√	√	X	√ (VPA, PB, PMD, CZP)	X	X	X	X	X	X	√	√ (WT)	X	X	X	√ (VPA, PB, Poly (more than 1 AED))	X
4	Iribanegaray D *et al.* [17]	√	√ (WT)	√	√	X	√ (VPA, PB)	X	X	X	X	X	X	√	√ (WT)	√	X	X	√ (PB)	X
5	Gray AL *el al.* [26]	X	√ (WT)	√	X	X	√ (VPA, PB, PHT, PB+PHT)	X	X	X	X	X	X	X	√ (WT)	X	X	X	√ (VPA, PB, PHT)	X
6	Graves NM *et al.* [18]	X	√	√	√	X	√ (PB, VPA, PHT, VPA)	√	√	X	X	X	X	X	√ (WT)	√	X	X	√ (PHT, PB, FBM, PHT+PB or FBM)	X
7	Reith DM *et al.* [19]	√	√ (WT, HT, BSA)	√	√	X	√ (VPA)	X	X	X	X	X	X	√	√ (BSA on CL, WT on V_d)	X	X	X	X	X
8	Chan E *et al.* [20]	X	√ (WT)	√	√	√	√ (PHT, PB, PHT and PB)	X	X	√	X	X	X	X	√ (WT)	√	X	X	√ (PB)	X
9	Deleu D *et al.* [27]	√	√ (WT)	√	√	X	X	X	X	X	X	X	√ (C_{ss})	X	X	X	X	X	X	√ (C_{ss})
10	Jiao Z *et al.* [29]	√	√ (WT)	√	√	X	√ (AED)	X	X	√	X	X	X	√	√ (WT on CL and V_d)	√ (>65 year)	X	X	√ (PHT, PB, VPA)	X

No	Study	Tested Covariates												Retained Covariates						
		CBZ dose	Body size	Age	Gender	Race	Co-medication	Smoking	Alcohol use	Dosage forms	Genotype	Laboratory value	Other	CBZ dose	Body size	Age	Gender	Race	Co-medication	Other
11	Jiao Z *et al.* [28]	√ (on CBZ and CBZ-E)	√ (WT on CBZ and CBZ-E)	√	√	X	√ (AEDs on CBZ and CBZ-E)	X	X	√	X	X	X	√ (on both CBZ and CBZ-E)	√ (WT on both CBZ and CBZ-E)	X	X	X	√ (VPA on both CBZ and CBZ-E, PHT, PB on CBZ)	X
12	Ahn JE *et al.* [14]	√ (for post TDM data)	√ (WT for both pre-TDM and post-TDM data)	X	X	X	X	X	X	X	X	X	X	√ (for post TDM data)	√ (WT for both pre-TDM and post-TDM data)	X	X	X	X	X
13	Vucicevic K *et al.* [21]	√	√ (WT)	√	√	X	√ (LTG, BZD, VPA, PB)	√	X	√	X	X	Allergy	√	√ (WT)	X	X	X	√ (VPA, PB)	X
14	Jankovic SM *et al.* [22]	√	√ (WT)	√	√	X	√ (VPA)	X	X	X	X	X	X	X	√ (WT)	√	X	X	√ (VPA)	X
15	Punyawudho B *et al.* [30]	X	√ (WT on CL, V_d, $K_{enz,out}$)	X	X	X	X	X	X	X	X	X	X	X	√ (WT on V_d)	X	X	X	X	X
16	Milovanovic JR *et al.* [31]	√	√ (WT)	√	√	X	√ (Pediatric: VPA, LTG) (Adult: PB, TPM, VPA, LTG)	X	X	X	X	X	X	√ (for both pediatrics and adults)	X	√ (for both pediatrics and adults)	X	X	√ (PB for adult population)	X
17	Punyawudho B *et al.* [32]	X	√ (WT, BMI, BSA, IBW, LBW)	√	X	√	√ (PHT)	√	√	X	X	√ (AST, ALT, ALB, BUN, SCr, CRCL, total protein)	Study center	X	X	X	X	X	√ (PHT)	X
18	EL Desoky ES *et al.* [23]	√	√ (WT)	√	√	X	√ (VPA, PHT, CZP, LTG)	X	X	X	X	X	Sampling time, CBZ conc., controlled vs uncontrolled epilepsy	X	X	X	X	X	X	X

No	Study	Tested Covariates												Retained Covariates						
		CBZ dose	Body size	Age	Gender	Race	Co-medication	Smoking	Alcohol use	Dosage forms	Genotype	Laboratory value	Other	CBZ dose	Body size	Age	Gender	Race	Co-medication	Other
19	Ding J *et al* [13]*	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
20	Kong ST *et al.* [24]	√	√ (WT)	√	√	√	√ (VPA)	X	X	X	X	√ (AST, ALP, GGT, ALB, TB, Hb, Hct)	age of seizure onset	√ (for both plasma and dried blood spot model)	X	X	√ (for plasma model)	X	X	X
21	Ahmed GF *et al.* [33]	X	√ (WT, BSA, IBW, LBW)	√	√	√	X	√	√	X	X	√ (AAG, ALB, TP)	grapefruit juice consumption, study center	X	√ (WT on V_d)	X	X	√ (on CL)	X	X
22	Djordjevic N *et al.* [34]	√	√ (WT)	√	√	X	√ (VPA)	X	X	X	√ (CYP1A2)	X	X	√	X	X	√	X	X	√ (CYP1A2)
23	Milovanovic DD *et al.* [35]	√	√ (WT)	√	√	X	√ (VPA)	X	X	X	√ (CYP2C8)	X	CBZ conc.	√	X	X	√	X	X	X

*Simulated datasets

AAG: alpha 1 acid glycoprotein, AED: antiepileptic drugs, ALT: alanine transaminase, ALB: albumin, ALP: alkaline phosphatase, AST: aspartate transaminase, BMI: body mass index, BUN: blood urea nitrogen, BSA: body surface area, BZD: benzodiazepine, CBZ: carbamazepine, CBZ-E: carbamazepine epoxide, CL: clearance, CR: control release, CRCL: creatinine clearance, C_{ss}: steady-state concentration, CZP: clonazepam, FBM: felbamate, GGT: gamma-glutamyl transferase, HT: height, Hb, hemoglobin, Hct: hematocrit, IBW: ideal body weight, IR: immediate release, $K_{enz,out}$: rate constant for enzyme degradation, LBW: lean body weight, LTG: lamotrigine, PB: phenobarbital, PHT: phenytoin, PMD: primidone, SCr: serum creatinine, TPM: topiramate, TB: total bilirubin, TP: total protein, V_d: volume of distribution, VPA: valproic acid, WT: weight

Table 4. Model structure, covariate-pharmacokinetic parameter relationship, inter-individual and residual variability and qualification of the population pharmacokinetic models of carbamazepine

No	Authors	Model structure	Equation	Model of IIV	Variability	Model of RV	Variability	Model evaluation
1	Martin ES *et al.* [15]	1-CMT with first order absorption and elimination	CL (L/h/kg) = 0.07442*LBW K_a (h^{-1}) = 0.4 (fixed) V_d (L) = 1.0 L/kg (fixed)	Additive after log transformed	%CV = 25.5	Combined	Proportional: %CV = 16.5 Additive: SD = 1.32 mg/L	No
2	Miller R *et al.* [25]	1-CMT with first order absorption and elimination	CL (L/h/kg) = 0.0522 V_d = 63.7 L (fixed) $K_{a,tablet}$ (h^{-1}) = 0.312 $K_{a,CR}$ (h^{-1}) = 0.149	Additive	%CV = 53.9	Additive	SD = 0.76 mg/L	No

No	Authors	Model structure	Equation	Model of IIV	Variability	Model of RV	Variability	Model evaluation
3	Yukawa E *et al.* [16]	Steady state model	CL (mL/h) = 64.9*WT (kg)$^{0.664}$* Dose (mg/kg/day)$^{0.465}$ * 1.07^{VPA} *1.16^{PB} *1.27^{POLY} (Poly = more than 2 antiepileptic drugs)	Proportional	%CV = 16.2	Additive	SD=1.05 mg/L	No
4	Iribanegaray D *et al.* [17]	1-CMT with first order absorption and elimination	CL (L/h) = (0.0122*WT + 0.0467*Dose (mg/kg/d) *Age$^{0.331}$ *(1+0.289*PB) K_a (h^{-1}) = 0.65 (fixed) V_d/F (L/kg) = 1.79 (fixed)	Proportional	%CV = 11.8	Additive	SD = 1.52 mg/L	external; N = 74
5	Gray AL *et al.* [26]	1-CMT with first order absorption and elimination	CL (L/h/kg) = (0.70 (WT)$^{0.40}$) *M (M=1 for monotherapy or concomitant with VPA, M = 1.43 for concomitant with PB or PHT) V_d (L) = 38.9 K_a (h^{-1}) = 0.34 (fixed)	Additive	14.3%	Additive	30.7%	No
6	Graves NM *et al.* [18]	1-CMT with first order absorption and elimination and a mixture model for hypometabolizers)	CL (L/h) = (0.0134 * WT + 3.58) * 1.42 (PHT) * 1.17 (PB or FBM) * 1.62 (PHT and PB or FBM) * 0.749 (age >= 70) V_d/F (L) = 1.97 * WT K_a (h^{-1}) = 0.441	Proportional	%CV = 26.2 %CV = 81.9 NR	Additive	SD = 1.82 mg/L	external; N = 50
7	Reith DM *et al.* [19]	1-CMT with first order absorption and elimination	CL/F (L/h) = (2.24 * surface area (m^2) +(0.047 * Dose (mg/kg)) V_d/F (L) = 0.37*WT (kg) K_a (h^{-1}) = 0.013	Exponential	%CV = 23.0 %CV = 247.2 %CV = 116.6	Additive	SD Assay 1 = 1.82 mg/L SD Assay 2 = 3.04 mg/L	bootstrap 200 runs
8	Chan E *et al.* [20]	Steady state model	CL (L/day/kg) = 40.7 * Age$^{0.494}$ * WT$^{-1.17}$ *1.44^{PB} (PB = 0 for CBZ monotherapy, 1 for co-medication with PB)	Exponential	%CV = 21.4	Exponential	%CV = 18.2%	external; N = 30
9	Deleu D *et al.* [27]	1-CMT with first order absorption and elimination	CL (L/h) = $\sqrt{\frac{(F*Dose)}{\tau}} * 8.41$ V_d (L) = 525	Proportional	20% 15%	NR	estimate = 0.0153	external; N = 13
10	Jiao Z *et al.* [29]	1-CMT with first order absorption and elimination	CL/F (L/h) = 0.072*Dose(mg/kg/d)$^{0.403}$*WT$^{0.697}$*1.45^{PHT}*1.17^{PB}*1.21^{VPA}* 0.851$^{(Age >65)}$ V_d/F (L) = 1.91 WT (kg) K_a (h^{-1}) = 1.2 (fixed)	Proportional	%CV = 15.9 %CV = 10.0 NA	Additive	SD = 0.987 mg/L	external; N = 40

No	Authors	Model structure	Equation	Model of IIV	Variability	Model of RV	Variability	Model evaluation
11	Jiao Z *et al*. [28]	1-CMT with first order absorption and elimination	For CBZ: CL/F (L/h) = 0.141*Dose (mg/d)$^{0.406}$ * WT (kg)$^{0.117}$*1.23^{VPA}*1.44^{PHT}*1.26^{PB}	Exponential	%CV = 10.3	Combined	Proportional: %CV = 14.5, Additive: SD = 0.45 mg/L	external; N = 40
			For CBZ: V_d/F (L) = 72.0		%CV = 42.9			
			For CBZ: K_a (h^{-1}) = 1.2 (fixed)		NA			
			For CBZ-E: CL/F (L/h) = 0.686*Dose(mg/d)$^{0.311}$*WT (kg)$^{0.44}$*0.693	Additive	4.75 L/h	Proportional	29.6%	
			For CBZ-E: V_d/F (L) = 175		Not estimated			
12	Ahn JE *et al*. [14]	1-CMT with first order absorption and elimination	K_a (h^{-1}) = 0.441 (fixed)	Exponential	NA	Proportional	%CV = 31.8 for all circumstances (pre TDM, post TDM with and without TDD)	No
			For pre TDM: CL (L/h) = 0.101 * WT		%CV = 54.6			
			For pre TDM: V_d (L) = 1.32 * WT		%CV = 61.4			
			For post TDM without TDD: CL (L/h) = 0.101 * WT		%CV = 54.6			
			For post TDM with TDD: CL (L/h) = 0.101 * WT * (TDD/1000)$^{1.15}$		%CV = 44.5			
			For post TDM without TDD: V_d (L) = 1.35 * WT		%CV = 63.6			
			For post TDM with TDD: V_d (L) = 1.33 * WT		%CV = 63.9			
13	Vucicevic K *et al*. [21]	1-CMT with first order absorption and elimination	CL/F (L/h) = 5.35 (Dose CBZ (mg/kg/d)/15)$^{0.591}$ * (1+0.414(Dose PB)/2) *(WT/70)$^{0.564}$ * 1.18^{VPA}	Exponential	%CV = 36.5	Additive	SD = 1.18 mg/L	external; N = 72
			V_d (L/kg) = 1.4 (fixed)		NA			
			$K_{a,IR}$ (h^{-1}) = 0.244 (fixed)		NA			
			$K_{a,CR}$ (h^{-1}) = 0.077 (fixed)		NA			
14	Jankovic SM *et al*. [22]	1-CMT with first order elimination (without absorption)	CL (L/h) = 1.73*WT$^{0.1}$ * Age$^{0.1}$ + 0.874*VPA	Exponential	16.8%	Exponential	%CV = 31.1	external; N = 16
			V_d (L) = 77.6		NR		NR	
15	Punyawudho B *et al*. [30]	1-CMT with hypothetical enzyme compartment	$\frac{dA_1}{dt} = k_0 - CL * C * A_2$ k_0 is the infusion rate (mg/h), C is the carbamazepine plasma conc (mg/L), A_2 is the proportion of enzymes at time t relative to the total enzymes at time zero in the hypothetical enzyme compartment. $\frac{dA_2}{dt} = k_{enz,in} * (1 - Factor) - k_{enz,out} * A_2$ $k_{enz,in}$ is the zero-order rate constant for enzyme production, $k_{enz,out}$is the first-order rate constant for the enzyme degradation, Factor is the fractional decrease of the enzyme production rate.					

No	Authors	Model structure	Equation	Model of IIV	Variability	Model of RV	Variability	Model evaluation
			Estimates of initial CL (L/h) = 3.05 $K_{enz,out}$ (h^{-1}) = 0.00805 Factor = 0.494	Exponential	%CV = 31.6	Proportional	%CV = 26.9	bootstrap and VPC
16	Milovanovic JR *et al.* [31]	1-CMT with first order elimination (without absorption)	Pediatric: CL/F (L/h) = 1.01+0.0667*Age + 0.0022 * Daily dose Adult: CL/F (L/h) = 1.15 + 0.0195 * Age + 0.0029 * Daily dose + 1.61 * PB	Exponential	%CV = 20.7 %CV = 11.4	Exponential	%CV = 5.1 %CV = 13.0	external; N=18 for pediatric and N= 13 for adult
17	Punyawudho B *et al.* [32]	1-CMT with first order absorption and elimination	CL/F (L/h) = 3.59*1.23 (PHT) V/F (L) = 102 K_a (h^{-1}) = 0.197	Exponential	%CV = 18.1 %CV = 74.7 NA	Proportional	%CV = 25.1	bootstrap
18	EL Desoky ES *et al.* [23]	1-CMT with first order absorption and elimination	CL (L/h) = 3.51 V (L) = 71.5 (fixed) $K_{a,susp}$ (h^{-1}) = 0.65 (fixed) $K_{a,CR}$ (h^{-1}) = 0.2 (fixed)	Proportional	%CV = 9.7 NR NR NR	Proportional	%CV = 81.4	bootstrap
19	Ding J *et al* [13]*	NA	NA	NA	NA	NA	NA	NA
20	Kong ST *et al.* [24]	1-CMT with first order absorption and elimination	CL/F (plasma) = 5.984*(Daily dose/ (WT *15))$^{0.5199}$ * 0.773^{SEX} Sex = 1 for female, 0 for male CL/F (DBS) = 0.9842*(Daily dose/WT)$^{0.6152}$ $K_{a,CR}$ (h^{-1}) = 0.47 (fixed) for DBS $K_{a,CR}$ (h^{-1}) = 0.47 (fixed) for plasma V_d/F (L) = 88 (fixed) for DBS V_d/F (L) = 66 (fixed) for plasma	Exponential Exponential	%CV = 0.2 %CV = 1.5 NA NA NA NA	Additive Additive	SD = 0.86 mg/L SD = 0.26 mg/L	external; N = 26
21	Ahmed GF *et al.* [33]	2-CMT with first order elimination (without absorption	Unbound CL (L/h) = 11.2*1.30^{RACE} V_1 (L) = 142*(WT/70) V_2 (L) = 175*(WT/70) Q (L/h) = 444 F_u = 0.25	Proportional Proportional Proportional Proportional Proportional	%CV = 32.2 %CV = 21.5 %CV = 23.5 %CV = 133.0 %CV = 18.9	Proportional (for unbound conc.) Combined (for total conc.)	17.8% Proportional: %CV = 15.5 Additive: SD = 0.002 mg/L	bootstrap and VPC

No	Authors	Model structure	Equation	Model of IIV	Variability	Model of RV	Variability	Model evaluation
22	Djordjevic N *et al*. [34]	1-CMT with first order elimination (without absorption	CL (L/h) = 0.176 + 0.0484*SEX + 0.019*CYP1A2 + 0.000156*CBZ dose	Exponential	%CV = 19.8	Exponential	%CV = 15.9	bootstrap
23	Milovanovic DD *et al*. [35]	1-CMT with first order elimination (without absorption)	CL (L/h) = 0.215 + 0.0696*SEX + 0.000183*CBZ dose	Exponential	%CV = 41.47	Exponential	%CV = 22.6	bootstrap

*This study did not perform model development. It was solely simulation-based study.

CBZ: carbamazpine, CBZ-E: carbamazepine epoxide, CL: clearance, CMT: compartment, CR: control release, CV: coefficient of variation, DBS: dried blood spot, F: bioavailability, FBM: felbamate, F_u: fraction unbound, IIV: inter-individual variability, IR: immediate release, k_a, absorption rate constant, k_e: elimination rate constant, $K_{enz,out}$: rate constant for enzyme degradation, LBW: lean body weight, NA: not applicable, NR: not report, PB: phenobarbital, PHT: phenytoin, Q: inter-compartmental clearance, RV: residual variability, SE: standard error, SD: standard deviation, SQRT: square root, Susp: suspension, TDD: total daily dose, TDM: therapeutic drug monitoring, V_d: volume of distribution, V_1: volume of distribution of central compartment, V_2: volume of distribution of peripheral compartment, VPA: valproic acid, VPC: visual predictive check, WT: weight