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Sources of lamotrigine pharmacokinetic variability: A systematic review of population pharmacokinetic analyses

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ABSTRACT

Background: Lamotrigine (LTG) is a new generation antiepileptic drug. However, relatively high interindividual pharmacokinetic variability of this drug has been documented. Therefore, several population pharmacokinetic studies of lamotrigine were conducted to identify factors influencing its pharmacokinetics.
Objective: This systematic review aimed to summarize significant factors influencing LTG pharmacokinetics and their relationships with pharmacokinetic parameters as well as the magnitude of pharmacokinetic variability.
Methods: Four databases i.e. PubMed, Scopus, CINAHL Complete, and Science Direct were systematically searched from their inception to March 2020. Population pharmacokinetic studies of LTG conducted in humans using a nonlinear-mixed effect approach were eligible for a systematic review.
Results: Nineteen studies were included in this systematic review. Most studies characterized LTG pharmacokinetics as a one-compartment model structure. The three most frequently identified significant covariates influencing LTG clearance included concomitant antiepileptic drugs, body weight, and genetic polymorphisms. Approximately 58% of the studies did not externally validate the models.
Conclusions: For clinical application, LTG maintenance dose could be optimized using population pharmacokinetic models employing covariates such as concomitant antiepileptic drugs, body weight, and genetic polymorphisms. However, these models should be assessed for their predictability in the target population before utilizing such models in clinical settings.

1. Introduction

Lamotrigine (LTG), a new generation antiepileptic drug (AED), is approved as adjunctive therapy for partial seizures as well as generalized seizures of Lennox-Gastaut syndrome in adult and pediatric patients aged ≥ 2 years. In addition, the drug is indicated for conversion from enzyme-inducing AED or valproate to monotherapy in adults with partial seizures and is also used for the maintenance treatment of bipolar I disorder [1]. It is also investigated for the treatment of treatment-resistant depressive disorders [2]. It exerts pharmacologic effects by inhibition of sodium [3,4] and calcium channels [4–6] leading to stabilization of the neuronal membrane. Moreover, it is thought to inhibit glutamate release [7] and the uptake of serotonin, dopamine, and noradrenaline [8]. These mechanisms are important for the pharmacological effects of lamotrigine in bipolar I disorder.

LTG is rapidly absorbed with time to peak concentrations within hours after a dose [4]. Its oral bioavailability is almost complete (98%) and not affected by food [1,4,9]. Approximately 55–68% of the drug is bound to plasma protein [10–12]. The reported volumes of distribution (V_d) range from 0.9 to 1.3 L/kg [13]. LTG is primarily metabolized by the liver via glucuronidation using uridine-diphosphate glucuronosyltransferase (UGT), mainly UGT1A4 and UGT2B7 [13–15]. The major metabolite, 2*N*-glucuronide is excreted via the kidney [12,14,15]. Both UGT1A4 and UGT2B7 are subject to genetic polymorphisms which might lead to variation in the elimination process [16–18]. Though LTG has not been shown to be an inducer or an inhibitor of hepatic mixed-function oxygenases, auto-induction was observed following multiple dosing to volunteers in the early stages of treatment [9,10]. However, such an effect might not be clinically relevant [9]. The average LTG clearances (CL_{LTG}) range from 0.35-0.59 mL/min, resulting in the corresponding half-life of 24-37 hours ([19]. Concurrent administration with enzyme-inducing AEDs such as phenobarbital, phenytoin, or carbamazepine decreases LTG half-life from 24 hours to approximately 15 hours ; whereas, co-administration with valproic acid, an enzyme

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inhibitor, increases LTG half-life to as much as 60 hours due to the competitive inhibition of glucuronidation [13,20].

In addition to drug interaction and genetic polymorphisms, other factors have been reported to influence LTG pharmacokinetics including body weight, gender, race, age group, duration of therapy and maternal status [10,19,21–23]. Regarding its safety, there has been reported that the toxicity from LTG therapy increases with increasing LTG levels, particularly at concentrations above 20 mg/L [24]. Altogether, these suggest the need to individualize drug therapy using therapeutic drug monitoring (TDM), especially in patients receiving hemodialysis, patients with severe liver impairment or pregnant women [25] and the well-accepted therapeutic range of LTG is between 2.5 to 15 mg/L [12].

Currently, LTG dosing is based on an escalation regimen categorized according to concurrent AED administration [1]. This approach; however, might not be appropriate in all patient populations and it is well established that population pharmacokinetics together with TDM data plays an important role in individualized drug therapy, by employing the Bayesian approach [26]. Several population pharmacokinetic studies of LTG with various influential predictors on its pharmacokinetic parameters have been reported [10,19,21–23,27–38,43,62]. Such factors together with Bayesian forecasting could support individualized LTG therapy. Therefore, we aimed to summarize significant factors influencing LTG pharmacokinetics through a systematic literature review. The population pharmacokinetic parameters of LTG as well as covariate-parameter relationships were also summarized.

2. Methods

2.1. Search strategy

Published population pharmacokinetic studies of LTG were systematically searched from PubMed, Scopus, ScienceDirect, and CINAHL Complete databases. The search was performed from inception to April 2020. The following search terms were employed: (lamotrigine OR LTG OR Lamictal) AND (“population pharmacokinet*” OR “nonlinear mixed effect” OR NONMEM)). Additional relevant studies from the reference lists of the identified articles were also examined to ensure the completeness of study identification.

2.2. Inclusion criteria and exclusion criteria

Population pharmacokinetics of LTG conducted in humans (both healthy volunteers and patients) were included in this systematic review. Other criteria for study inclusion were: utilizing a nonlinear-mixed effect approach for population pharmacokinetic analyses and providing sufficient information on model development as well as population pharmacokinetic parameter estimates. The exclusion criteria for this review were: 1) review articles, methodology studies, expert opinions or case reports, 2) studies with only model simulations based on published population pharmacokinetic models, and 3) studies published in a non-English language. Screening of the titles and abstracts of the non-redundant articles were independently performed by both reviewers. For an article without an abstract, a full-text screen was performed. A consensus for the inclusion of the identified articles was made.

2.3. Data extraction

Extracted information included 1) study design (e.g. prospective or retrospective study), study site, number of study centers, and sample size of the population, 2) characteristics of the population (e.g. proportion of male and female, body size, age, ethnicity, underlying disease, concurrent medication), 3) dosage regimens and information relating to pharmacokinetics (e.g. LTG daily dose, dosing frequency, formulations, route of administration, sample collection strategy (sparse or extensive), sampling time, and drug assay, and 4) methodology of population pharmacokinetics (e.g. model structure, estimation method, statistical models (i.e. interindividual and residual variability), and covariate models), 5) the estimates of fixed and random effects and 6) methods used for model evaluation. We classified model evaluation into 3 categories according to the classification described by Brendel et al [39], that is, 1) basic internal evaluation i.e. goodness of fit plots, and precision of the parameter estimates, represented as % relative standard error (%RSE) or 95% confidence interval (95% CI), 2) advanced internal evaluation e.g. bootstrap analysis and simulation-based approaches such as visual predictive check (VPC), prediction-corrected visual predictive check (pcVPC), normalized prediction distribution error (NPDE), and 3) external evaluation in which an external dataset was used to evaluate the model.

2.4. Quality assessment

The checklist developed by Kanji et al [40] which is the reporting guidelines for clinical pharmacokinetic studies was used to assess the quality of the published population pharmacokinetic models of LTG. Moreover, selected checklist items created by Dartois et al [41] and Abdel-Jalil et al [42] were also employed for quality assessment.

3. Results

3.1. Study identification

A total of 1,068 non-redundant articles were identified from the systematic search. Title and abstract screening removed 918 articles as not relevant. Of the remaining 150 articles, 19 articles, published between 1997 and 2019, were included in this systematic review according to the inclusion and exclusion criteria. This review followed the PRISMA checklist for systematic reviews. A PRISMA diagram of the study selection is presented in Fig. 1.

3.2. Study characteristics

Among the 19 selected articles [10,19,21–23,27–38,43,62], the ultimate goals of most studies were to determine the impacts of demographic and physiologic determinants on the pharmacokinetics of LTG as well as to provide population estimates of pharmacokinetic parameters. Five studies aimed to determine the effect of genetic polymorphisms of the UGT isoenzymes or transporters on LTG pharmacokinetics [29,36,37,43,62]. In terms of the study design, ten studies were retrospectively conducted using data from medical records or pooled clinical trials [10,19,21,22,28,30,31,33–35], whereas nine studies were prospectively conducted for population pharmacokinetic purposes [23,27,29,32,36–38,43,62]. The sample sizes of the participants ranged from 38 to 600, with a median of 125. Most studies reported concomitant administration with other AEDs. Four studies [10,22,36,43] determined the influence of oral contraceptive on CL_{LTG}. One did not provide information on concurrent medications [23]. The population characteristics of the included studies are summarized in Table 1.

3.3. Pharmacokinetic data

The number of LTG samples used for population pharmacokinetic analyses ranged from 40 to 2,407, with approximately 1-10 samples per patient. Only two studies utilized data obtained from both sparse and intensive sampling strategy [19,62]. The analytical assay for LTG was performed using high-performance liquid chromatography (HPLC) in all studies except a study by Grasela et al [10] in which immunofluorometric assay (IFA) was utilized. The LTG dose ranged from 2 to 1,400 mg/d. Table 2 summarizes dosing regimens, sampling strategy as well as an analytical method of the the included studies.

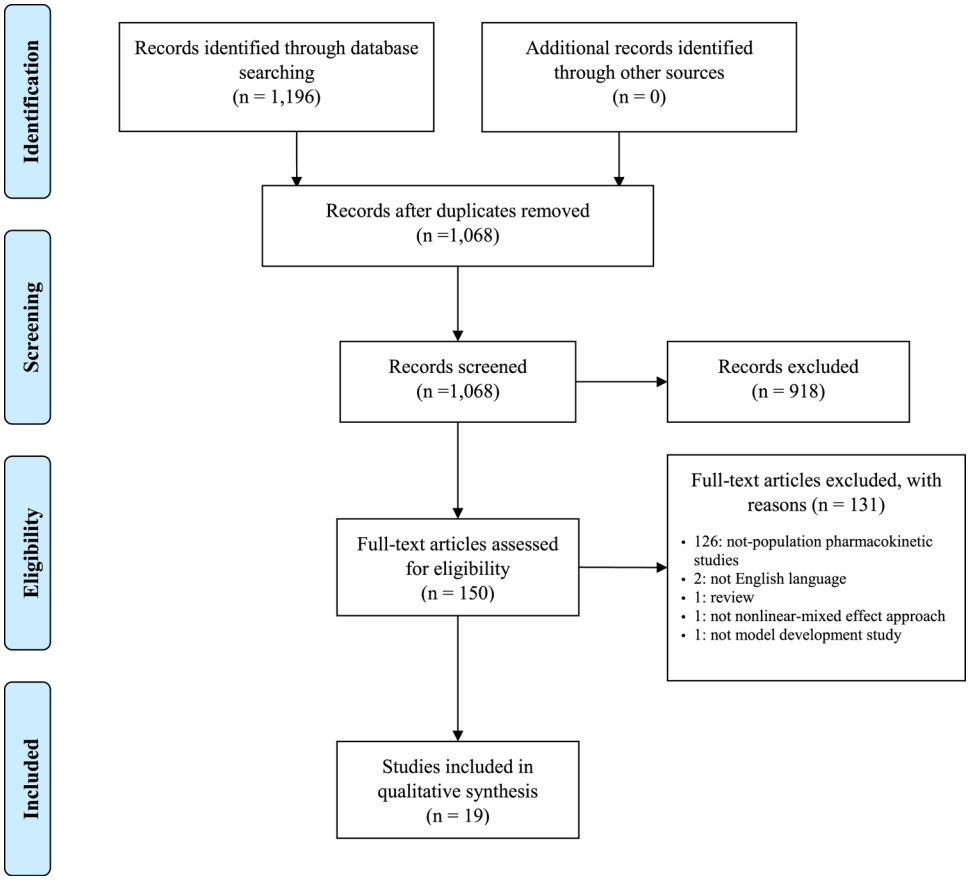

Fig. 1. A PRISMA diagram of the study identification.

3.4. Population pharmacokinetic analyses

Except for one study in which P-Pharm software was utilized [28], all other studies used NONMEM software for the population pharmacokinetic analyses. For the structural model, most studies employed a one-compartment model with first-order absorption and elimination, except three studies where a steady-state model [30], a mixture model during a pregnant period [23], and a one-compartment without absorption process [33] were employed. Only five studies reported the estimated absorption rate constant (K_a) of the immediate-release dosage form, with the values ranging from 1.09 to 3.18 h^{-1} [10,19,21,22,43]. Other studies fixed the K_a at the literature values of either 1.3 or 3.5 h^{-1}. One study estimated the K_a of the extended dosage form with a value of 0.0087 h^{-1}. The estimated V_d of LTG ranged from 0.35 to 2.48 L/kg. Three studies fixed the V_d at published values of 1.2 or 1.5 L/kg because of the insufficient information during the distribution phase [27,35,37]. Regarding the elimination process, the estimated CL_{LTG} ranged from 0.705-4.23 L/h (Fig. 2).

Covariate modeling was mostly performed using stepwise forward addition and/or backward elimination. The impact of body size was tested in all studies. Co-medication and age are the second most investigated covariates (18 studies), followed by an effect of gender (14 studies), laboratory values (6 studies) e.g. amino alanine transferase (ALT), aspartate aminotransferase (AST), serum creatinine (SCr), blood urea nitrogen (BUN), genetic polymorphisms (5 studies), LTG dose (5 studies), race (4 studies), and duration of therapy (4 studies). Two studies determined the influence of the study center on LTG pharmacokinetics [28,34]. Other covariates screened included smoking status [34,43,62], formulation (i.e. immediate release and extended-release) ([19], and alcohol consumption [34]. The most common significant predictor for CL_{LTG} was concomitant medication, found in 17 studies, accompanied by weight (13 studies). Further, polymorphisms, duration of LTG therapy, race, age, LTG dose, renal function, and smoking also significantly influenced CL_{LTG} (Fig. 3). For V_d, a significant effect of weight was identified in four studies [10,21,31,43]. In addition, one study found a significant impact of gender on V_d [10]. Table 3 summarizes investigated and significant covariates on LTG pharmacokinetics.

Regarding the methods used for pharmacokinetic parameter estimation, seven studies did not provide information on the estimation method [10,23,28,30,31,33,38], two studies used first-order estimation [21,22], one studies employed first-order conditional estimation with Laplacian [35], and the rest utilized first-order conditional estimation with interaction method [19,21,27,32,34,36,37,43,62].

The interindividual variability was most commonly modeled with exponential (12 studies) and proportional (7 studies) relationships. The

Table 1
Demographic data of the included studies.

No	Author, year	Study design	Study site	Patient characteristics	Race	N (male)	Mean age (range)	Mean weight (range)	Concomitant medication
1	Hussein et al, 1997 [22]	Retrospective from phase II/III clinical trials	Multicenter	Epileptic patients with normal hepatic and renal function	Caucasian and Asian	163 (81)	(14-76 y)	(40.5-106.5 kg)	OCT
2	Grasela et al, 1999 [10]	Retrospective (from 3 add-on placebo-controlled phase 2-3 trials in patients with refractory partial seizures	Multicenter	Adults with epilepsy	Non-Caucasian, Caucasian	527 (238)	34 ± 10 y (18-64 y)	73.5 ± 18.0 kg (38.2-159.0 kg)	CBZ, PHT, PRM, PB, OCT
3	Chen et al, 2000 [21]	Retrospective • For model development: 3 clinical trials • For model validation: 4 clinical trials	NR	Children with epilepsy, partial seizures, or Lennox-Gastaut syndrome	NR	202 (114) 148 (82)	8.9 y* (3.4-15 y)** 7.6 y* (2.6-17 y)**	27 kg* (14-56 kg)26 kg (12-71 kg)	VPA and/or 1 IND
4	Gidal et al, 2000 [30]	Retrospective (reviewed from medical and pharmacy records)	NR	Children and adults with mental retardation, developmental disabilities and epilepsy	NR	62 (33)	33.6 ± 11.3 y (10-61 y)	47.0 ± 9.9 kg	CRP, CZP, DZP, ETS, FBM, GBP
5	Chan et al, 2001 [28]	Retrospective	Multicenter (South and Western Australia)	Epileptic patients	NR	129 (65)	34.2 y (17-71 y)	NR	CBZ, CZP, CLO, ETS, GBP, PB PMD, TPM, VGB,
6	Punyawudho et al, 2008 [34]	Retrospective (from randomized double blind parallel group monotherapy comparison of LTG, gabapentin, and CBZ in epileptic elderly)	NR	Elderly newly diagnosed with seizures	American Indian: 3 Black: 46 White: 99	148 (143)	70.64 y (59-92 y)	80.88 kg (40-123 kg)	PHT
7	Rivas et al, 2008 [35]	Retrospective	Multicenter (Spain and Germany)	Spanish and German adult epileptic patients	White	Spanish: 103 (63) German: 497 (274)	38 y (26.8-51.3 y) 39 y (32-49 y)	70 kg (61.8-77 kg) 76 kg (65-85 kg)	CBZ, LEV, PB, PHT, PRM, VPA, VPA + IND
8	Milovanovic et al, 2009 [33]	Retrospective	Single site	Children and adult patients with epilepsy	White	38 (17)	25.78 ± 13.15 y (7-62 y)	65.3 ± 21.58 kg (28-112 kg)	CBZ, PB, TPM, VPA,
9	He et al, 2012 [31]	Retrospective	Single site	Children with epilepsy have normal liver and kidney function	Asian	116 (68)	0.5-17 y	27.9 kg (8-85 kg)	CBZ, CZP, LEV, OXC, PB, TPM, VPA
10	Mallaysamy et al, 2013 [32]	Prospective	Single site	Adult epileptic patients	Asian	95 (75)	35 y (18-60 y)	62 kg (38-82 kg)	CBZ, VPA
11	Singkham et al, 2013 [36]	Prospective	Single site	Adult and elderly with epilepsy	Asian	75 (43)	48 y (18-82 y)	63 kg (36-98 kg)	CBZ, OCT, PHT, VPA
12	Brzakovic et al, 2014 [27]	Prospective	Single site	Adult and pediatric epileptic patients treated with LTG + CBZ and/or VPA	White	53 (23)	13.4 ± 8.52 y (3-35 y)	47 ± 24.5 kg	CBZ, VPA, CBZ + VPA
13	Polepally et al, 2014 [23]	Prospective	Single site	Pregnant epileptic and or psychiatric patients	Whites, Black, Asian, Native Americans	64 (0)	31.1 ± 535 y (17-42 y)	64.3 ± 12.7 kg	NR
14	Milosheska, 2016 [43]	Prospective	Single site	Adult epileptic patients	White	100 (30)	39.8 y* (20.7-80.4 y)	70 kg* (50-124 kg)	CBZ, OCT, OXC, PB, PHT, STL, VPA
15	Zhang et al, 2017 [38]	Prospective	Single site	Chinese epileptic children	Asian Infant, toddler, preschool School age Adolescence	388 166 152 70	 4 y (0.58-6 y) 9 y (6.1-11.96 y) 13 y (12-17.62 y)	 16.25 kg (7.5-28 kg) 30 kg (16-77.5 kg) 51.5 kg (25-98 kg)	CBZ, CZP, LEV, OXC, PB, TPM, VPA
16	Chen et al, 2018 [29]	Prospective	Single site	Chinese epileptic children	Asian	121 (71)	11 y* (2-16 y)	40 kg* (10-110 kg)	CZP, LEV, OXC, TPM, VPA,

(*continued on next page*)

Table 1 (*continued*)

No	Author, year	Study design	Study site	Patient characteristics	Race	N (male)	Mean age (range)	Mean weight (range)	Concomitant medication
17	van Dijkman et al, 2018 [19]	Retrospective	NR	Children, adult and elderly with epilepsy	NR	494 (248)	45.3 ± 24.2 y (0.2-91 y)	70.3 ± 27.5 kg (3-151.9 kg)	CBZ, CLO, CLP, GBP, LEV, OXC, PB, PHT, TPM, VPA
18	Xu et al, 2018 [37]	Prospective	Single site	Chinese epileptic children	Asian	182 (111)	Median: 8 y (2-18 y)	Median: 27 kg (10-73 kg)	VPA, CBZ, OXC, LEV, TPM, BZD
19	Wang et al, 2019 [62]	Prospective	Single site	Chinese epileptic patients (children to adults)	Asian	89 (42)	28 y (4-63 y)	59 kg (15-94 kg)	VPA, RFP, VPA + RFP

BZD:benzodiazepine, CBZ: carbamazepine, CLO: clobazam, CLP: clozapine, CRP: clorazepate, CZP: clonazepam, DZP: diazepam, ETS: ethosuximide, FBM: felbamate, GBP: gabapentin, IND: enzyme inducers, LEV: levetiracetam, NR: not report, OCT: oral contraceptive, OXC: oxcabazepine, PB: phenobarbital, PHT: phenytoin, PRM: primidone, RFP: rifampicin, STL, sertraline, TPM: topiramate, VGB: vigabatrin, VPA: valproic acid.

* Median.

** 5-95 percentile.

magnitudes of variability on CL_{LTG} and V_d across studies ranged from 21.3% to 52.35% and 7% to 115.8%, respectively. For the residual variability, the most commonly used function was a proportional relationship, followed by a combined additive and proportional, and an additive relationship, with the extent of variability, ranged from 5.7% to 45.7%.

For model qualification, the basic internal evaluation was employed in all studies. Of these, five and three studies utilized advanced [23,27,34,36,43] or external [21,31,33] evaluation in addition to the basic internal approach. Five studies used all evaluation methods [29,19,37,38,62]. The software, estimation methods, model structure, and model evaluation are presented in Table 4. Table 5 summarizes parameter-covariate relationships, interindividual and residual variability.

3.5. Quality assessment

Approximately 52.6% of the study, did not specify the route of administration in the title/abstract section. Three studies did not describe the pharmacokinetic background of LTG. The highest missing information of the methodology section was LTG formulation (15 studies), followed by sample storage (12 studies) and frequency of administration (12 studies). Methodology on population pharmacokinetic analyses was sufficiently reported in all studies, except the estimation method which was not specified in seven studies. For the discussion/conclusion section, most studies did not report the external validity of their findings (11 studies) and study limitations (7 studies). In addition, most studies published before 2014 did not declare the potential conflicts of interest and funding. The quality of the included studies can be found in supplementary data.

4. Discussion

Population pharmacokinetics is an essential approach used to characterize factors influencing drug pharmacokinetics in diverse populations. Although TDM is not mandatory for LTG therapy, studies have shown that the drug exhibits high pharmacokinetic variability [20,44,45]. To our knowledge, this is the first systematic review that summarizes population pharmacokinetics of LTG and information in this review can be used to guide LTG dosing regimens.

4.1. Absorption

LTG is rapidly absorbed with the estimated K_a values ranging from 1.09 to 3.18 h^{-1}, which is consistent with the results from traditional pharmacokinetic studies in healthy subjects [13]. No studies identified any significant predictors on K_a. Though the effect of food on LTG pharmacokinetics are well defined [1], other demographic determinants might affect the absorption process such as age or gender. Evidence has shown that advancing age is associated with reduced absorption of several substances [46]. In addition, the difference in transit times between men and women has also been reported [47]. For future research on population pharmacokinetics of LTG, such factors should be further investigated.

4.2. Distribution

In most studies, LTG pharmacokinetics was characterized as a one-compartment structural model. The estimated V_d from population pharmacokinetics ranged from 0.35 to 2.48 L/kg, wider than that obtained from traditional pharmacokinetic analyses (0.9-1.3 L/kg) [13]. Significant factors affecting V_d of LTG were weight [21,31,38,43], gender [10], alkaline phosphatase (ALP) [29], and *ABCG2*-34AA (rs2231137), *MDR1*-2677TT (rs2032582) and *MDR1*-C3435TT (rs1045642) genotypes [62]. An increase in V_d with an increase in body weight was observed which is not surprising given that subjects with

Table 2
Dosing regimens, sampling strategy, and analytical methods.

No	Author, Year	Dose/day	Dose range	Frequency	Mean LTG concentration	Concentration range	Dosage form	Sampling strategy	Sampling time	Samples per patient	Total samples	Assay
1	Hussein et al, 1997 [22]	Trial 1: 100 mg OD for the first week then 150 mg OD for 2 weeks Trial 2, 3: 50 mg OD for the first week then 20 mg bid for week 2, then 50 mg in the morning and 100 mg in the evening (week)	50-150 mg/d	1-3 per day	NR	NR	Tablet, capsule	NR	Vary (spread within the dosing intervals starting from 0.5 h)	NR	NR	HPLC
2	Grasela et al, 1999 [10]	Fixed dose (300-500 mg/day) or dose titration: (100,200,300 400 mg/day	NR	NR	NR	NR	Tablet, capsule	NR	Trough concentration	NR	2407	IFA
3	Chen et al, 2000 [21]	Varied according to 7 protocols (single fixed dose, and multiple titrated dose)	For titrated dose: 50-400 mg/day or 1.5-15 mg/kg/day	1-2 per day	NR	NR	NR	Sparse	Vary (according to each protocol)	1-6	652	HPLC, IFA
4	Gidal et al, 2000 [30]	369 ± 236 mg/d or 8.1 ± 5.9 mg/kg/d	50-1200 mg/day or 1-36 mg/kg/day	NR	6.8 mg/L	NR	NR	Sparse	Trough	1	62	HPLC
5	Chan et al, 2001[28]	NR	12.5-850 mg/day	1-4 per day	NR	NR	NR	Sparse Extensive	9.33 ± 5.29 (h) NR	1-8 for sparse 12-70 for extensive	629	HPLC
6	Punyawudho et al, 2008 [34]	titrated as follows: 25 mg/day * 2 week, then 50 mg/day *2 week, then 100 mg/day * 1 week, then 150 mg/day	NR	NR	NR	NR	NR	Sparse	NR	6 (calculated)	875	NR
7	Rivas et al, 2008 [35]	Spanish: 200 mg/day	100-300 mg/day	1-2 per day	4.1 mg/L	2.7-8.0 mg/L	NR	Sparse	as clinically required and at trough concentration	1-5	204	HPLC
		German: 350 mg/day	200-500 mg/day	1-2 per day	6.4 mg/L	4.4-9.4 mg/L	NR	Sparse	as clinically required and at trough concentration	1-5	1495	
8	Milovanovic et al, 2009 [33]	160.94 ± 95.16 mg/day	12.5-500 mg/day	1-2 per day	4.63 mg/L	0.50-10.88 mg/L	Tablet	Sparse	Trough (9-12 h after dose, 72%), peak (28%)	1 (calculated)	40	HPLC
9	He et al, 2012 [31]	135 mg/day	12.5-525 mg/day	NR	5.52 mg/L	0.14-17.89 mg/L	NR	Sparse	Trough	1.65 (1-10)	191	HPLC
10	Mallaysamy et al, 2013 [32]	Median 200 mg/day	25-400 mg/day	NR	NR	0.4-11.9 mg/L	NR	Sparse	NR	1-6 (Median: 3)	237	HPLC
11	Singkham et al, 2013 [36]	106.7 mg/day	25-400 mg/day	NR	NR	NR	NR	Sparse	Trough (most data)	1.5 (calculated)	116	HPLC
12	Brzakovic et al, 2014 [27]	94.1 ± 53.5 mg/day	NR	1 or 3 per day	4.36 mg/L	NR	Tablets	Sparse	Trough	1.3 (calculated)	70	HPLC
13	Polepally et al, 2014 [23]	NR	50-1400 mg/day	2 per day	NR	NR	NR	NR	Vary(according to visit)	9.3 (calculated)	600	HPLC
14	Milosheska et al, 2016 [43]	Median: 200 mg/day	50-600 mg/day	NR	NR	0.7-23.18 mg/L	NR	Sparse	Peak (2-4 h) and trough	2	200	HPLC
15	Zhang et al, 2017 [38]	4.53 mg/kg/day (Infant, toddler, preschool age)	1.61-16.67 mg/kg/day	NR	5.57 mg/L	0.44-19.97 mg/L	NR	Sparse	Trough	1-2 (calculate)	206	HPLC
		3.75 mg/kg/day (school age)	1.5-12.38 mg/kg/day	NR	5.63 mg/L	0.51-19.79 mg/L	NR	Sparse	Trough	1-2 (calculate)	243	HPLC
		3.88 mg/kg/day (adolescence age)	2-13.64 mg/kg/day	NR	4.76 mg/L	0.61-20.79 mg/L	NR	Sparse	Trough	1-2 (calculate)	90	HPLC
16	Chen et al, 2018 [29]	Median: 3.77 mg/kg/d	0.23-12.50 mg/kg/day	NR	4.49 mg/L (Median)	0.21-19.35 mg/L	NR	Sparse	Trough	2.29 (calculated)	277	HPLC
17	van Dijkman et al, 2018 [19]	255 ± 190 mg/day	2-1200 mg/day	NR	NR	NR	NR	Sparse and Extensive	NR	NR	NR	NR

(*continued on next page*)

Table 2 (*continued*)

No	Author, Year	Dose/day	Dose range	Frequency	Mean LTG concentration	Concentration range	Dosage form	Sampling strategy	Sampling time	Samples per patient	Total samples	Assay
18	Xu et al, 2018 [37]	Median: 50 mg/day	25-225 mg/d	NR	4.76 mg/L (Median)	0.36-20.60 mg/L	NR	NR	Trough	2.1 (calculated)	376	HPLC
19	Wang et al, 2019 [62]	118 mg/day	6.25-300 mg/d	Various throughout the study	NR	NR	NR	Sparse and Extensive	Trough and other time	4.7 (calculated)	419	HPLC-MS/MS

HPLC: high-performance liquid chromatography, HPLC-MS/MS: High-performance liquid chromatography-electrospray ionization tandem mass spectrometry, IFA: Immunofluorometirc assay, LTG: lamotrigine, NR: not report.

higher body weight would have higher total body water and LTG thoroughly distributes through the total body water [48]. For the effect of gender, the V_d is approximately 27% lower in women compared to men [10]. In general, males exhibit higher total body water, extracellular water, intracellular water, as well as blood and plasma volumes. Therefore, for a water-soluble drug, a higher V_d in males is generally observed [47]. Regarding the effect of genetic polymorphisms on V_d, patients with the *ABCG2*-34AA genotype had a 42.0% decrease in V_d, whereas patients with the *MDR1*-2677TT and *MDR1*-C3435TT genotypes had a 136% increase in Vd [62]. Since ABCG2 is an efflux transporter widely expressed in several tissues such as small intestine, blood-brain barrier, and liver canalicular membranes [49], the clinical relevance of this association is not explicit. The lower V_d would result in the lower LTG concentrations, while the higher V_d would cause the opposite. In both cases, the simulated LTG concentrations from this study were within the recommended therapeutic range of 3-15 mg/L according to the AGNP guideline [50]. Therefore, dosage adjustment based on these polymorphisms might not be necessary.

4.3. Elimination

The CL_{LTG} is affected by several physiologic and demographic determinants. Of these, bodyweight is the most commonly identified significant covariate on $CL_{LTG.}$ As expected, in most studies, CL_{LTG} increases with increasing body weight which could be explained by the correlation between the size of the excretion organ and bodyweight. However, different relationships between CL_{LTG} and the bodyweight among studies were reported. Specific conclusions on the best relationship could not be drawn due to different population characteristics and other covariates investigated.

Co-administration of LTG with enzyme inducers (e.g. carbamazepine, phenytoin, primidone, phenobarbital, oxcarbazepine) increased CL_{LTG}. While an enzyme inhibitor such as valproic acid resulted in the opposite effect which could be explained by its competitive inhibition of glucuronidation [51]. However, the magnitudes of these effects varied across study populations and the number of concomitant medications. Comparisons of the extents of drug-drug interaction among studies are beyond the scope of this review.

Three studies identified significant effects of *UGT2B7* polymorphisms [29,36,43] and one study reported a significant effect of *SLC22A1*-1222AA (rs628031) polymorphisms [62] on CL_{LTG}. Milosheska et al [43] reported a 20% lower CL_{LTG} in patients carrying *UGT2B7*-161TT (rs7668258). In accordance with these findings, a study conducted in Thai epileptic patients showed that patients carrying *UGT2B7*-161CT or TT had 18% lower CL_{LTG} compared with those carrying *UGT2B7*-161CC [36]. Also, Chen et al [29] showed a 21% decreased in CL_{LTG} in patients carrying *UGT2B7*-161CT. Nonetheless, such an effect is relatively small and its clinical relevance should be further investigated. In addition, Milosheska et al [43] also found that patients carrying *UGT2B7*-372AG or GG (rs28365063) had 19% and 117% higher CL_{LTG}, respectively. Although the *UGT2B7*-372GG showed a massive effect, patients carrying this genotype are rare and routine monitoring of this polymorphism is not recommended. Further, a study by Wang et al [62] reported a 52% decrease in CL_{LTG} in patients carrying *SLC22A1*-1222AA which may necessitate a dose reduction.

Hussein et al [22] and Grasela et al [10] found that Non-Caucasians had 25% and 28.7% lower CL_{LTG} than Caucasians, respectively. Nonetheless, the application of this covariate in a clinical situation should be further investigated since no scientific rationale could support such findings. Therefore, dose adjustment should be based on clinical response rather than ethnic difference.

Polepally et al found a significant influence of gestational age on CL_{LTG} by employing a mixture model [23]. Based on this model, pregnant women were classified into two groups (i.e. fast and slow clearance). During pregnancy, CL_{LTG} linearly increased at two different rates i.e. 0.118 L/h and 0.0115 L/h per week of gestation. The author

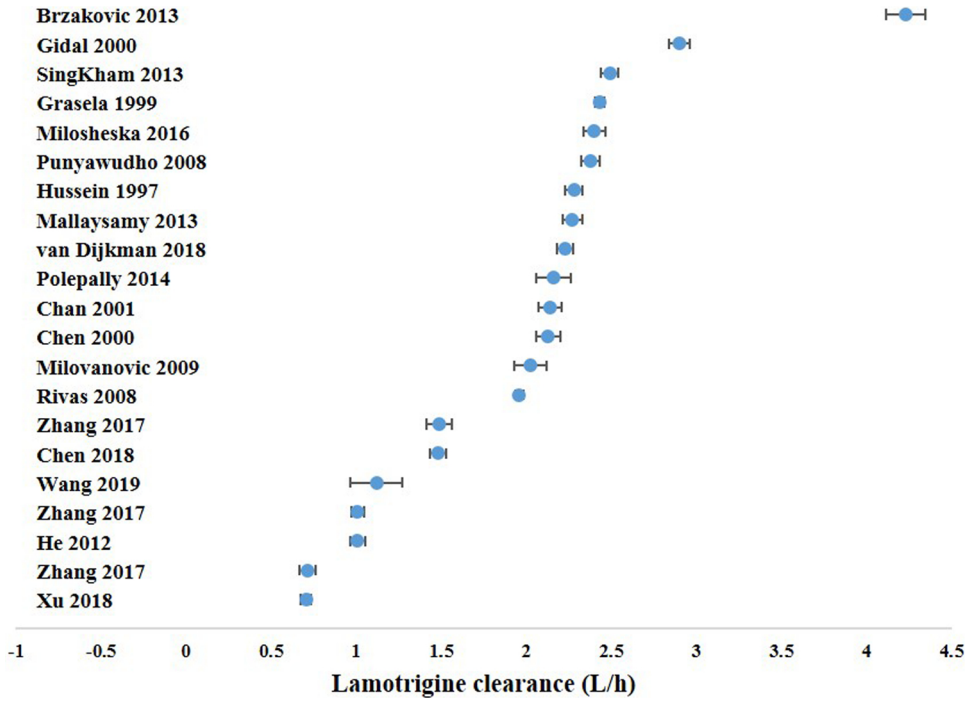

Fig. 2. Estimated lamotrigine clearance of the included studies.

proposed that the difference in CL_{LTG} between two groups might be due to genetic variations in *UGT1A4*. However, this assumption should be further investigated and LTG dosage adjustment should be carefully performed. After the delivery, CL_{LTG} declined exponentially with the first-order rate constant of 1.27 per week, reaching the baseline value within 3 weeks and dosage reduction should be done accordingly. Further, van Dijkman et al utilized an integrated model incorporating a maturation function to characterize age-related changes in LTG disposition across various age groups ranging from 0.2-91 years [19]. This study identified a 15% lower in CL_{LTG} in subjects aged > 65 years and about 31.5% higher in CL_{LTG} corrected for body weight in a child aged 1.7 years. Although LTG has not been approved for children aged < 2 years, these results provide substantial important information for future clinical trials.

The effect of smoking status on LTG pharmacokinetics was investigated in three studies. Though Punyawudho et al [34] and Wang et al [62] did not find a significant effect of smoking status, Milosheska et al identified that smoking significantly increased CL_{LTG} by 34% compared to non-smoking [43], which is in agreement with a study by Reinsberger et al [52]. Discrepancies in the smoking effect observed from these population pharmacokinetic studies probably are due to a different degree of smoking among studies. Studies have shown that cigarette smoke induces both CYP450 and UGTs [53]. However, providing that LTG is not mediated by CYP450 1A2, the major isoform induced by smoking [54], the effect of cigarette smoke on CL_{LTG} could be mediated by either UGT1A4 or UGT2B7. Nonetheless, evidence has shown that tobacco smoking might not have a significant impact on UGT1A4 [52]. Therefore, the observed increase in CL_{LTG} could be due to the UGT2B7.

Four studies determined the influence of the duration of therapy on

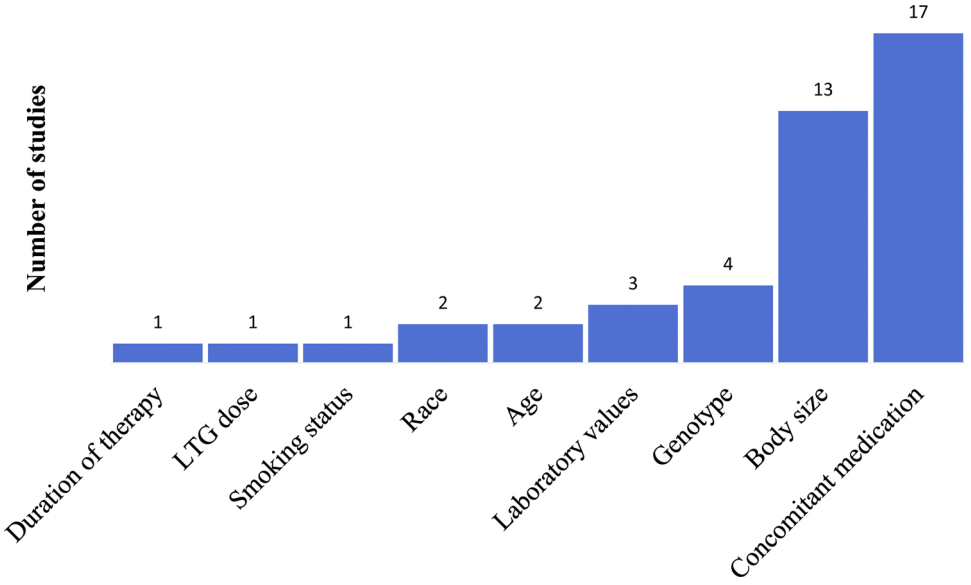

Fig. 3. Significant covariates identified from the included studies.

Table 3
Tested and significant covariates of the population pharmacokinetic models.

No	Author, year	Tested									Retained								
		Parameter	Concomitant drug	Race	Sex	Age	Body size	Dose	Genotype	Other	Parameter	Concomitant drug	Race	Sex	Age	Body size	Dose	Genotype	Other
1	Hussein et al, 1997 [22]	CL	OCT	✓	✓	✓	WT	✓		duration of therapy	CL		✓						duration of therapy
2	Grasela et al, 1999 [10]	NR	OCT, No. of AED (CBZ, PHT, PMD, PB)	✓	✓	✓	WT			duration of therapy, BE of tablet and capsule	CL	OCT, No. of AED (CBZ, PHT, PMD, PB)	✓			WT			
3	Chen et al, 2000 [21]	CL	AED	✓	✓	✓	WT				CL	VPA, VPA + at least 1 IND				WT			
		V					WT				V					WT			
4	Gidal et al, 2000 [30]	CL	VPA, IND, conc. of VPA, CBZ, PHT, PB		✓	✓	WT			tube feeding	CL	Presence of 1 or > 1 IND				WT			
5	Chan et al, 2001 [28]	CL	VPA, PHT, CBZ, PB, VGB, TPM, ETS, CLO, CZP, GBP, PMD,		✓	✓				clinical site (South or Western Australia)	CL	VPA, PHT							
6	Punyawudho et al, 2008 [34]	CL	PHT	✓		✓	WT, BMI, BSA, IBW, LBW			study center, smoking, alcohol use, lab (ALB, BUN, BUN/CR ratio, SCr, CLcr, AST, ALT), duration of therapy	CL	PHT				WT			BUN/CR ratio
7	Rivas et al, 2008 [35]	CL	VPA, LEV, CBZ, PB, PHT, PMD		✓	✓	WT				CL	VPA, PHT, PB or PMD, CBZ, IND				WT			
8	Milovanovic et al, 2009 [33]	CL	VPA, CBZ, PB, TPM		✓	✓	WT	✓			CL	CBZ, VPA				WT	Daily dose		
9	He et al., 2012 [31]	CL, V	VPA, OXC, CZP, LEV, TPM, CBZ, PB		✓	✓	WT				CL	VPA, CBZ, PB				WT			
10	Mallaysamy et al, 2013 [32]	CL	VPA, CBZ		✓	✓	WT				CL	VPA, CBZ				WT			
11	Singkham et al, 2013 [36]	CL, V	PHT, CBZ, OCT, VPA		✓	✓	WT		*UGT1A4*-142T > G, *UGT2B7* 372A > G,-161C > T	lab (AST, ALT, SCr)	CL	VPA, IND						*UGT2B7*	
12	Brzakovic et al, 2014 [27]	CL, V	VPA, CBZ, CBZ + VPA, CBZ dose, VPA dose			✓	WT	✓			CL	CBZ + VPA, VPA				WT			
13	Polepally et al, 2014 [23]	CL				GA, MA	maternal body size			postpartum week, indication (epilepsy or no epilepsy)	CL				GA				postpartum week

(*continued on next page*)

Table 3 (*continued*)

No	Author, year	Tested									Retained								
		Parameter	Concomitant drug	Race	Sex	Age	Body size	Dose	Genotype	Other	Parameter	Concomitant drug	Race	Sex	Age	Body size	Dose	Genotype	Other
14	Milosheska et al, 2016 [43]	CL	CBZ, OXC, PHT, PB, OCT, VPA, STL		✓	✓	WT, IBW	✓	*UGTs, SLC22A1, ABCB1*	smoking, SCr, CLcr, AST, ALT	CL	VPA or STL, CBZ, PB, PHT				WT		*UGT2B7*	smoking, CL_{CR}
15	Zhang et al, 2017 [38]	CL, V	VPA, CBZ, OXC, PB		✓	✓	WT				CL	VPA, combination with IND				WT			
											V					WT			
16	Chen et al, 2018 [29]	CL	VPA, OXC, CZP, TPM, LEV			✓	WT, HT, BMI	✓	*UGT1A4, UGT2B7, ABCB1, ABCG2, SLC22A1, HNF4alpha*	ALT, AST, gamma-GT, ALP, SCr, Serum cystatin C	CL	VPA daily dose, OXC				WT		*UGT2B7*-161C > T	ALP
17	van Dijkman et al, 2018 [19]	CL	CBZ, CLO, CZP, GBP, LEV, OXC, PB, PHT, TPM, VPA			✓	WT			formulation (IR, XR)	CL	CBZ, PHT, VPA			Elderly				E_{MAT}
18	Xu et al, 2018 [37]	CL	VPA, VPA dose, VPA conc, OXC, LEV, CBZ, TPM,		✓		WT, BMI	✓	*UGT1A4* -142T > G, *UGT2B* -161C > T, *UGT2B7* -802C > T	LTG dose Lab (ALT, AST, Scr, CL_{CR}), duration of therapy	CL	VPA conc.				WT			
19	Wang et al, 2019 [62]	CL, V	VPA, RFP, VPA + RFP		✓	✓	WT		*UGT1A4, UGT2B7, MDR1, ABCG2, ABCC2, SLC22A1*	renal function, smoking	CL	VPA, RFP						*SLC22A1*, *MDR1*-2677TT	

AED: antiepileptic drug, ABCB1: ATP-binding cassette protein B1, ABCG2: ATP-binding cassette protein G2, ABCC2: ATP-binding cassette protein C2, ALB: albumin, ALT: alanine aminotransferase, ALP: alkaline phosphatase, ATP-binding cassette protein B1, AST: aspartate aminotransferase, BE: bioequivalence, BMI: body mass index, BSA: body surface area, BUN: blood urea nitrogen, CBZ: carbamazepine, CLO: clobazam, CL: clearance, CL_{CR}: creatinine clearance CR: creatinine, CZP: clonazepam, CZP: clonazepam, E_{MAT}: maturation process parameterized using sigmoidal function, ETS: ethosuximide, GA: gestational age, GBP: gabapentin, gamma-GT: Gamma-glutamyltransferase, HT: height, HNF4alpha: hepatocyte nuclear factor 4 alpha, IBW: ideal body weight, IND: enzyme inducers, IR: immediate release, LBW: lean body weight, LEV: levetiracetam, MA: maternal age, MDR: multi drug resistance, OCT: oral contraceptive, OXC: oxcarbazepine, PB: phenobarbital, PHT: phenytoin, PMD: primidone, RFP: rifampicin, SCr: serum creatinine, SCL22: solute carrier family 22, STL: sertraline, TPM: topiramate, UGT: Uridine 5'-diphospho-glucuronosyltransferase, V: volume of distribution, VPA: valproic acid, VGB: vigabatrin, WT: weight, XR: extended release.

Table 4
Software, estimation methods, model structure and evaluation.

No	Author, Year	Software	Model	Estimation Method	Evaluation
1	Hussein et al, 1997 [22]	NONMEM version 6 level 2.0	1 CMT first order absorption and elimination	FO	Basic internal (GOF, precision of estimates)
2	Grasela et al, 1999 [10]	NONMEM version 4	1 CMT first order absorption and elimination	NR	Basic internal (GOF, precision of estimates)
3	Chen et al, 2000 [21]	NONMEM	1 CMT first order absorption and elimination	FO	Basic internal (GOF, precision of estimates) and external
4	Gidal et al, 2000 [30]	NONMEM version 4.0	Steady state model	NR	Basic internal (precision of the estimates)
5	Chan et al, 2001 [28]	P-Pharm version 1.4	1 CMT first order absorption and elimination	NR	Basic internal (precision of the estimates)
6	Punyawudho et al, 2008 [34]	NONMEM version 5.0	1 CMT first order absorption and elimination	FOCE-I	Basic internal (GOF) and advanced internal (bootstrap and predictive check)
7	Rivas et al, 2008 [35]	NONMEM version 5.0	1 CMT first order absorption and elimination	FOCE with Laplace	Basic internal (GOF, precision of estimates)
8	Milovanovic et al, 2009 [33]	NONMEM version 5.0	1 CMT with first order elimination (without absorption)	NR	Basic internal (GOF, precision of estimates) and external (N = 15)
9	He et al, 2012 [31]	NONMEM version 5.0	1 CMT first order absorption and elimination	NR	Basic internal (GOF, precision of estimates) and external
10	Mallaysamy et al, 2013 [32]	NONMEM version 6.0	1 CMT first order absorption and elimination	FOCEI	Basic internal (GOF, precision of estimates)
11	Singkham et al, 2013 [36]	NONMEM version 6.0	1 CMT first order absorption and elimination	FOCEI	Basic internal (GOF, precision of estimates) and advanced internal (bootstrap and predictive check)
12	Brzakovic et al, 2014 [27]	NONMEM version 7.2	1 CMT first order absorption and elimination	FOCEI	Basic internal (GOF, precision of estimates) and advanced internal (bootstrap and NPC)
13	Polepally et al, 2014 [23]	NONMEM version 7.0	A steady state infusion model for preconception and mixture model for pregnant period	NR	Basic internal (GOF, precision of estimates) and advanced internal (bootstrap and standardized VPC)
14	Milosheska, 2016 [43]	NONMEM version 7.3	1 CMT first order absorption and elimination	FOCEI	Basic internal (GOF, precision of estimates) and advanced internal (bootstrap and VPC)
15	Zhang et al, 2017 [38]	NONMEM version 5	1 CMT first order absorption and elimination	NR	Basic internal (GOF, precision of estimates), advanced internal (bootstrap and NPDE) and external
16	Chen et al, 2018 [29]	NONMEM version 7	1 CMT with first order absorption and elimination	FOCEI	Basic internal (GOF, precision of estimates), advanced internal (bootstrap, NPDE) and external
17	van Dijkman et al, 2018 [19]	NONMEM verions 7	1 CMT with first order absorption and elimination	FOCEI	Basic internal (GOF, precision of estimates), advanced internal (bootstrap, VPC, NPC, NPDE) and external
18	Xu et al, 2018 [37]	NONMEM verions 7.3	1 CMT with first order absorption and elimination	FOCEI	Basic internal (GOF, precision of estimates), advanced internal (bootstrap, NPDE) and external
19	Wang et al, 2019 [62]	NONMEM version 7	1 CMT with first order absorption and elimination	FOCEI	Basic internal (GOF, precision of estimates), advanced internal (NPDE) and external

CMT: compartment, FO: first-order estimation, FOCE: first-order conditional estimation, FOCE-I: first-order conditional estimation with interaction, GOF: goodness of fit, NPC: numerical predictive check, NPDE: normalized prediction distribution error, NR: not report, VPC: visual predictive check.

Table 5
Parameter-covariate relationships, interindividual and residual variability.

No	Author, Year	Parameter			IIV		RV	
		K_a	V_d	CL	Relationship	% CV	Relationship	% CV
1	Hussein et al, 1997 [22]	K_a (h^{-1}) = 3.18	V/F (L) = 77.4	CL/F (L/h) = 2.28*(1 + race*(-0.287))*(1-0.338*$e^{(-0.119*time)}$) Race = 0 for Caucasian, 1 for Asian	Proportional	K_a: inestimable V: 33.6 CL:32.1	Proportional	20.8
2	Grasela et al, 1999 [10]	K_a (h^{-1}) = 1.30	V (L) = 132*(1-0.265*Sex)	CL (mL/min) = (10.5 + 0.428*WT)*(1-0.254*race)*(1 + 0.131*NAED) Race = 0 for Caucasian, 1 for non-Caucasian NAED: 0 if receiving 1 or fewer AED NAED: 1 if receiving 2 or more AED	Proportional	K_a:77.5 F: not estimated V: 44.3 CL:32.2	Proportional	23
3	Chen et al, 2000 [21]	K_a (h^{-1}) = 1.09	V (L)= 2.12 * WT	CL (mL/min)= (19.3 + 0.598*WT)(1-0.605*BAL)(1-0.772VPA) BAL: 1 for at least IND + VPA, 0 otherwise VPA: 1 for VPA without IND, 0 otherwise	Proportional	K_a: 156.5 V: 51.0 CL: 50.9	Proportional	24.1
4	Gidal et al, 2000 [30]	NA	NA	**FOR VPA = 0:** CL/F (mL/min) = 0.176*$WT^{0.6}$ + 2.19*IND + 3.20*POLY **FOR VPA > 0:** CL/F (mL/min) = 0.063*$WT^{0.6}$ + 2.19*IND + 3.20*POLY POLY: more than one IND	Proportional	CL: 24.1	Additive	SD = 0.77 mg/L
5	Chan et al, 2001 [28]	K_a (h^{-1}) = 3.57 (fixed)	V/F (L) = 78.1 ± 5.1	CL/F (L/h) = 2.14 ± 0.81	Proportional	K_a: not estimated V: 7 CL: 38	Proportional	38
6	Punyawudho et al, 2008 [34]	K_a (h^{-1}) = 3.5 (fixed)	V/F (L) = 115	CL/F (L/h) = (0.0332*BUN/CR ratio + 0.0268*WT)*1.59 (if patients take PHT)	Exponential	K_a: not estimated V: not estimated CL: 34.2	Combined	19.8 SD = 0.31 mg/L
7	Rivas et al, 2008 [35]	K_a (h^{-1}) = 1.3 (fixed) F = 1.0 (fixed)	V_d (L/kg) = 1.5 (fixed)	CL (L/h) = 0.028*WT*$exp^{(-0.713*VPA)}$*$exp^{(0.663*PHT)}$*$exp^{(0.588*PB\ or\ PMD)}$*$exp^{(0.467*CBZ)}$*$exp^{(0.864*IND)}$	Proportional	K_a: not estimated V_d: not estimated CL: 27.49	Additive	SD = 1.25 mg/L
8	Milovanovic et al, 2009 [33]			CL (L/h) = 0.615 + (0.01*TBW) + (0.00445*DD) + (1.13*CBZ)-(1*VPA) DD = total daily dose	Exponential	CL: 29.55	Exponential	21.31
9	He et al, 2012 [31]	K_a (h^{-1}) = 1 (fixed) F = 1.0 (fixed)	V_d (L) = 16.7*(TBW/27.87)	CL (L/h) = 1.01*(TBW/27.87)$^{0.635}$*$exp^{-0.753*VPA}$*$exp^{0.868*CBZ}$*$exp^{0.633*PB}$	Exponential	CL: 25.8 V_d: not estimated	Proportional	21.21
10	Mallaysamy et al, 2013 [32]	K_a (h^{-1}) = 0.38	V/F (L) = 56.3	CL/F (L/h) = 2.27(1 + 0.466)^{CBZ}(1-0.383)^{VPA}(1 + 0.0124)(WT-median)	Exponential	V: 30.6 CL: 28.8	Combined	Prop: 5.7 SD = 0.127 mg/L
11	Singkham et al, 2013 [36]	K_a (h^{-1}) = 1.3 (fixed)	V/F (L) = 156	CL/F (L/h) = 2.49*(1 + 1.04*IDC)*(1-0.41VPA)*(1-0.18*_UGT2B7_-161C > T) IDC and VPA: 1 for those using an enzyme inducing agent and VPA, 0 otherwise	Exponential	K_a: not estimated V: not estimated CL: 22.42	Combined	Prop: 26.11 SD = 0.18 mg/L
12	Brzakovic et al, 2014 [27]	K_a (h^{-1}) = 3.5	V/F (L/kg) = 1.2 (fixed)	CL/F (L/h) = 4.23*(1-0.695*COTH1)*(1-0.876*COTH2)*1.69^{WT60}*0.775^{WT25} COTH1 = 1 if concomitant with CBZ and VPA COTH2 = 1 if concomitant with VPA WT60 = 1 for patient WT > = 60 WT25 = 1 for patient WT < =25	Exponential	CL: 42.2	Proportional	42.66

(*continued on next page*)

Table 5 (*continued*)

No	Author, Year	Parameter			IIV		RV	
		K_a	V_d	CL	Relationship	% CV	Relationship	% CV
13	Polepally et al, 2014 [23]			Preconception: CL/F (L/h) = 2.16 Pregnant: CL/F (L/h) = 2.16+0.118*GA Pregnant: CL/F (L/h) = 2.16+0.0115*GA Postpartum: CL/F (L/h) = deltaCL*exp$^{(-1.27*PPW)}$ + 2.16 deltaCL: CL/F change from baseline to delivery PPW: postpartum weeks	Exponential	CL: 40.6 slopes: 43.0	Proportional	45.7
14	Milosheska et al, 2016 [43]	K_a (h^{-1}) = 1.96	V_d (L) = 76.2*(1+0.0181(WT-70))	CL (L/h) = 2.40*(1-0.579INH)*(WT/70)$^{0.938}$*(1+0.340Tob)*(1+0.546IND)*(11-0.0358*UGT2B7*-161CT)*(1-0.204*UGT2B7*-161TT)*(1+0.194*UGT2B7*-372AG)*(1+1.17*UGT2B7*-372GG)*(1+0.00328(CLcr-110))	Exponential	K_a: 71.1 V: 30.1 CL: 33.1	Proportional	18.0
15	Zhang et al, 2017 [38]	K_a (h^{-1}) = 1.3 (fixed)	V_d/F (L) = 10.4 (Infant, toddler, preschool age)	CL/F (L/h) = 0.715*(WT/16.25)$^{0.655}$*0.458^{VPA}*1.99^{IND}	Exponential	CL: 30.21	Proportional	SD = 3.22 mg/L
			V_d/F (L) = 17.7 (school age)	CL/F (L/h) = 1.01*(WT/30)$^{0.399}$*0.465^{VPA}*1.98^{IND} (school age)		CL: 24.29		SD = 2.73 mg/L
			V_d/F (L) = 23.1 (adolescence age)	CL/F (L/h) = 1.49*(WT/51.5)$^{0.509}$*0.498^{VPA}*1.7^{IND}		CL: 31.06		SD = 0.737 mg/L
			V_d/F (L) = 16.7*(WT/25)$^{0.919}$ (whole age)	CL/F (L/h) = 0.945*(WT/25)$^{0.645}$*0.463^{VPA}*1.94^{IND}		CL: 28.46		SD = 3.02 mg/L
16	Chen et al, 2018 [29]	K_a (h^{-1}) = 3.5 (fixed)	V/F (L)= 115*exp$^{(1.25*(1-ALP/213))}$	CL/F (L/h) = 1.48(WT/40)$^{0.596}$*exp$^{[(VPA/500)*(-0.619)]}$*exp$^{0.271*OXC}$*(1-0.218**UGT2B7*-161C > T)	Exponential	CL: 25.8	Proportional	26.6
17	van Dijkman et al, 2018 [19]	$K_{a,IR}$ (h^{-1}) = 2.43 $K_{a,XR}$ (h^{-1}) = 0.0087	Vd/F (L/kg) = 1.97(WT/70)	CL/F = (2.23(WT/70)$^{0.75}$*E_{MAT}*E_{ELD}*E_{CBZ}*E_{PHT}*E_{VPA} E_{MAT} = E_{ELD}: = 0.852 if PT age > 65 E_{CBZ}: 1.765 if CBZ is co-administered E_{PHT}: 2.29 if PHT is co-administered E_{VPA}: 0.536 if VPA is co-administered	Exponential	K_{aIR}: 78.03 K_{aXR}: 67.82 V: 79.12 CL:52.35	Combined	Prop: 39.5 SD = 0.236 mg/L
18	Xu et al, 2018 [37]	K_a (h^{-1}) = 3.57 (fixed)	Vd/F (L/kg) = 1.2 (fixed)	CL/F (L/h) = 0.705(WT/27)$^{0.574}$*(1-0.273*CVPA/62.1)	Exponential	CL: 21.3	Combined	Prop: 26.8 SD = 0.857 mg/L
19	Wang et al, 2019 [62]	K_a (h^{-1}) = 1.97 (fixed)	V/F (L) = 12.7*$E_{ABCG-34AA}$*$E_{MDR1-2677TT+C3435TT}$	CL/F (L/h) = 1.12*E_{VPA} *E_{RFP}*$E_{SLC22A1-1222AA}$ E_{VPA}: 0.624 if VPA is co-administered E_{RFP}: 0.1647 if RFP is co-administered $E_{SLC22A1-1222AA}$: 0.475 if $_{SLC22A1-1222AA}$ is present	Proportional	V: 115.8 CL:73.5	Combined	Prop: 22.4 SD = 41.0 mg/L

ABCG: ATP-binding cassette protein G, AED: antiepileptic drug, CBZ: carbamazepine, CL: clearance, CV: coefficient of variation, CVPA: concentration of valproic acid, F: bioavailability, IIV: interindividual variability, IND: enzyme inducers, INH: inhibitor, K_a: absorption rate constant, MDR: multi drug resistance, NA: not applicable, OXC: oxcarbazepine, PB: phenobarbital, PHT: phenytoin, PMD: primidone, POLY: more than one IND, RFP: rifampicin, RV: residual variability, SCL22: solute carrier family 22, SD: standard deviation, TBW: total body weight, Tob: tobacco smoking, V_d: volume of distribution, VPA: valproic acid, WT: weight.

CL_{LTG} to investigate an autoinduction effect [10,22,34,37] and only one study found a significant association between the duration of therapy and CL_{LTG}, with a 17% increase in CL_{LTG} over the 48-week duration [22]. In addition, Milovanovic et al investigated an autoinduction property using LTG daily dose as a covariate and found that LTG daily dose had a significant effect on CL_{LTG} [33]. Similar findings have been reported in classical pharmacokinetic studies. However, this effect is minimal and of negligible clinical relevance [9,55]. Therefore, no dosage adjustment is recommended.

Hepatic metabolism is the major route of LTG elimination [12]. Nonetheless, Punyawudho et al [34] and Milosheska et al [43] showed a significant influence of renal function on CL_{LTG} using BUN/SCr ratio and creatinine clearance (CL_{CR}), respectively. In both cases, CL_{LTG}, decreased as the renal function declined. This could be explained by the extrahepatic metabolism via UGT since UGT is also expressed in other tissues including the esophagus (UGT1A7, UGT1A8, and UGT1A10), stomach (UGT1A7, UGT1A10), bile duct (UGT1A10), and colon (UGT1A8, UGT1A10) [56–61].

4.4. Quality assessment and model evaluation

The methodology of population pharmacokinetic analyses was adequately reported in most studies. However, some information on pharmacokinetic data e.g. sample storage, formulation details, and sampling time was not defined. These details are of importance for concluding the validity of the findings. Therefore, for future population pharmacokinetic studies, implementation of the reporting guidelines [40–42] specified in our review is recommended. In terms of model generalizability, only half of the studies externally evaluated the models using external datasets. From a clinical perspective, an external evaluation of the models using the target population is recommended before applying such models in clinical situations.

5. Conclusion

Population pharmacokinetics of LTG was well described with a one-compartment model and pharmacokinetic variability of LTG could be explained by concomitant AEDs, body weight, genetic polymorphisms, age, and race. About 58% of the studies were not externally evaluated, therefore the generalizability of these models should be assessed.

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Author contributions

JM and NL planned and designed the systematic review. JM drafted the initial manuscript and revised the subsequent drafts. Both authors read and approved the final version of the manuscript.

Declaration of Competing Interest

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

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.seizure.2020.07.014.

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