Bridging the Medication Adherence Gap from Therapeutic Drug Monitoring: A Bayesian approach for Anti-Seizure Medications

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Supplementary files

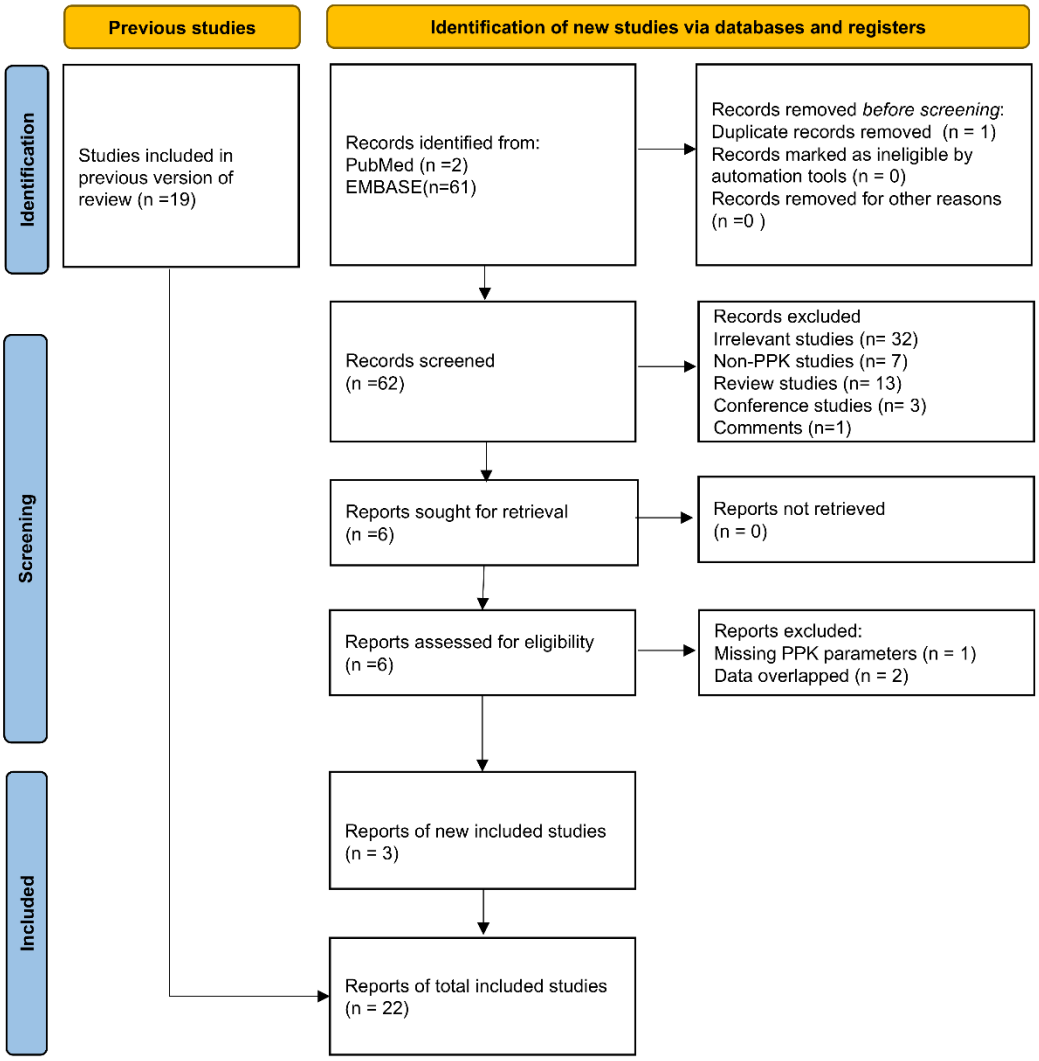
Appendix 1. The updated identification of population pharmacokinetic studies.

The population pharmacokinetic (PPK) models of commonly used antiseizure medications (ASMs) have been retrieved in our previous study[1], including carbamazepine, lamotrigine, eslicarbazepine acetate, levetiracetam, oxcarbazepine, phenobarbital, topiramate, valproic acid, clobazam, and zonisamide.

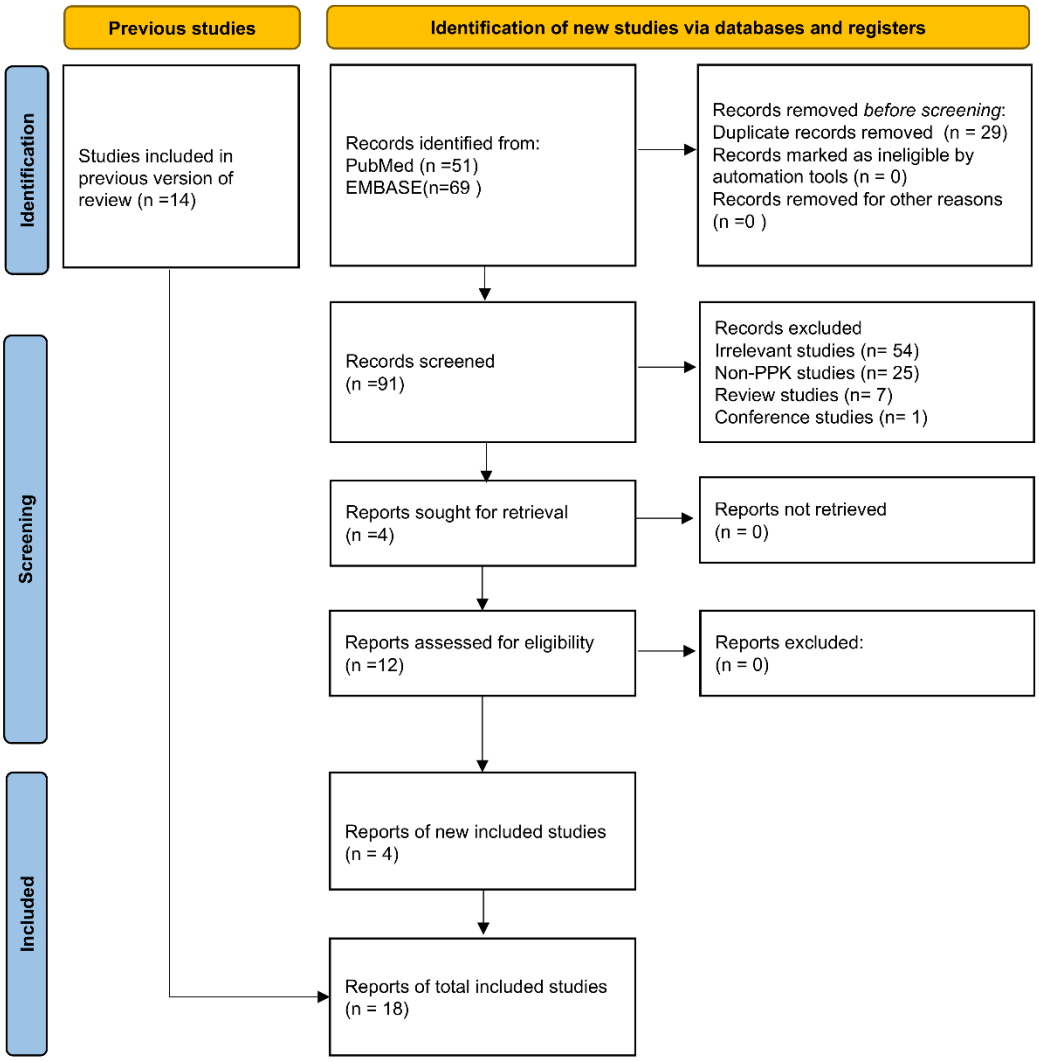
Therefore, updated literature research was performed for these ASMs from 31 March, 2022 to 30 November, 2024. The PPK population PK studies were identified using the following search terms: "drug name" and 'population pharmacokinetic', 'pharmacokinetic modeling', 'nonlinear mixed effect model', 'NONMEM', 'WINNONMIX', 'P-PHARM', 'nlmixed', 'NLME', 'USC*PACK' or 'MONOLIX'. Furthermore, the reference lists of the chosen articles were reviewed to uncover any pertinent studies. The literature search was conducted independently by two authors. In cases of disagreement, a third senior investigator was consulted for resolution. The updated literature was selected if they enrolled more participates compared with the previously identified PPK studies, or based on the judgement from the researchers.

After screening, there is no newly published PPK models of carbamazepine, clobazam, eslicarbazepine acetate, phenobarbital and zonisamide from 31 March, 2022 to 30 November, 2024. The updated PRISMA flow diagram for the identification of PPK studies of lamotrigine, levetiracetam, oxcarbazepine, topiramate and valproic acid were shown below.

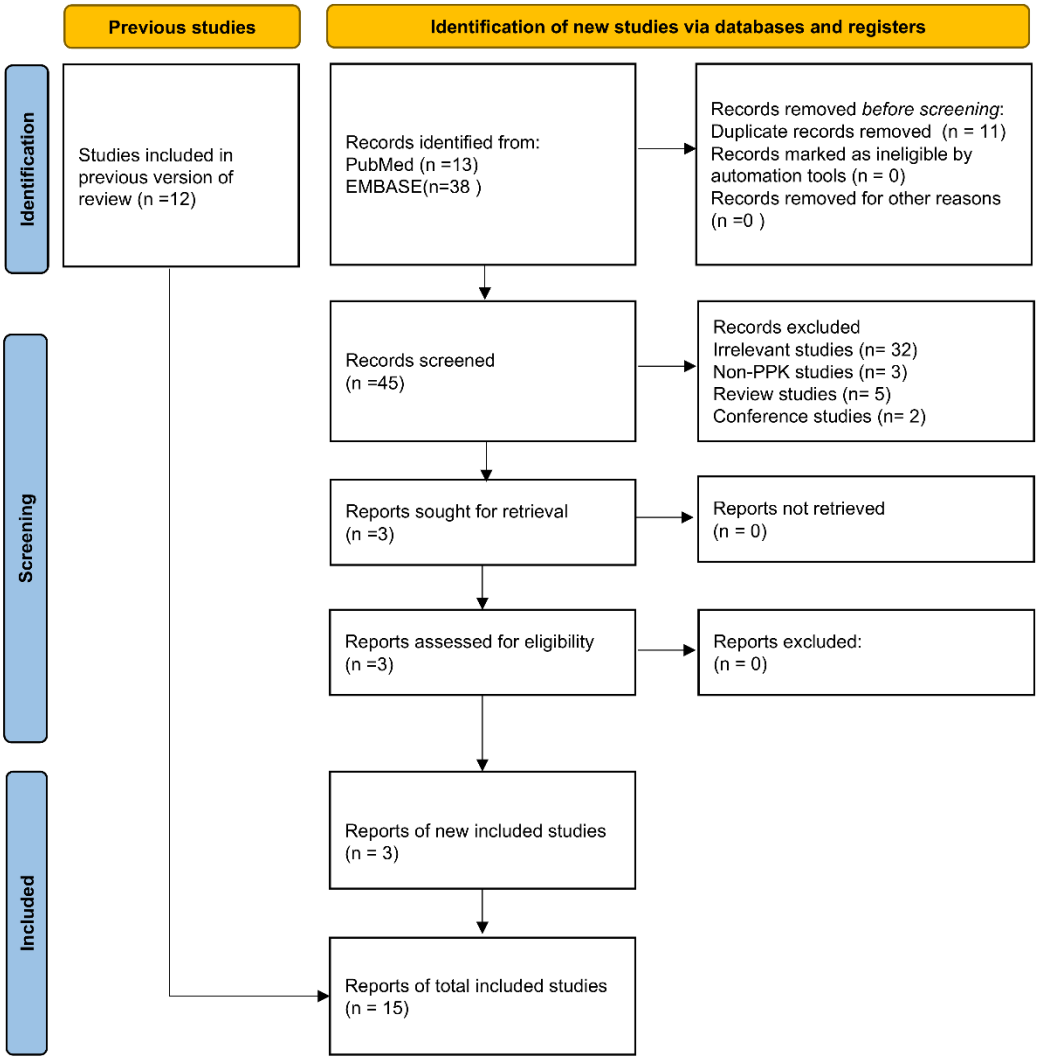
PRISMA flow diagram for identifying population pharmacokinetic studies of lamotrigine



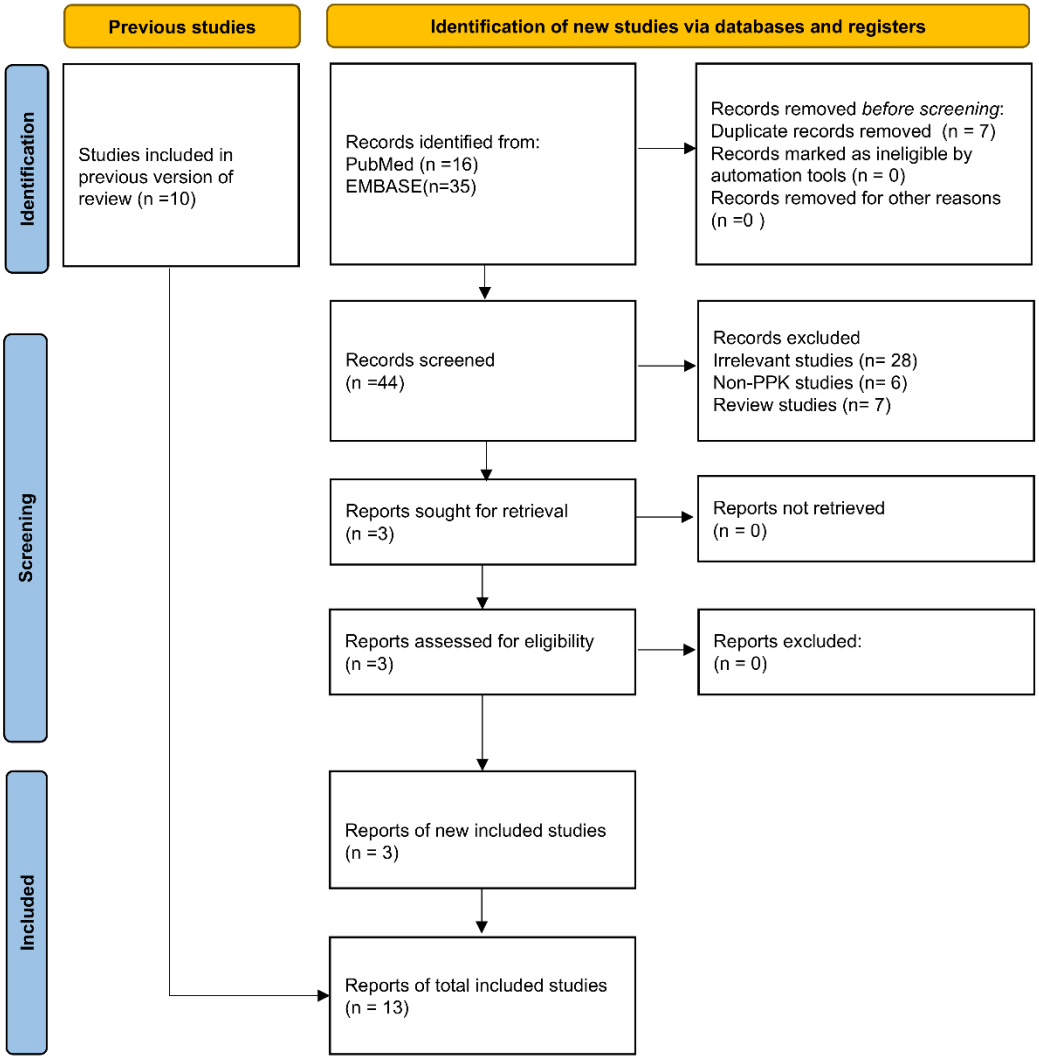
PRISMA flow diagram for identifying population pharmacokinetic studies of levetiracetam



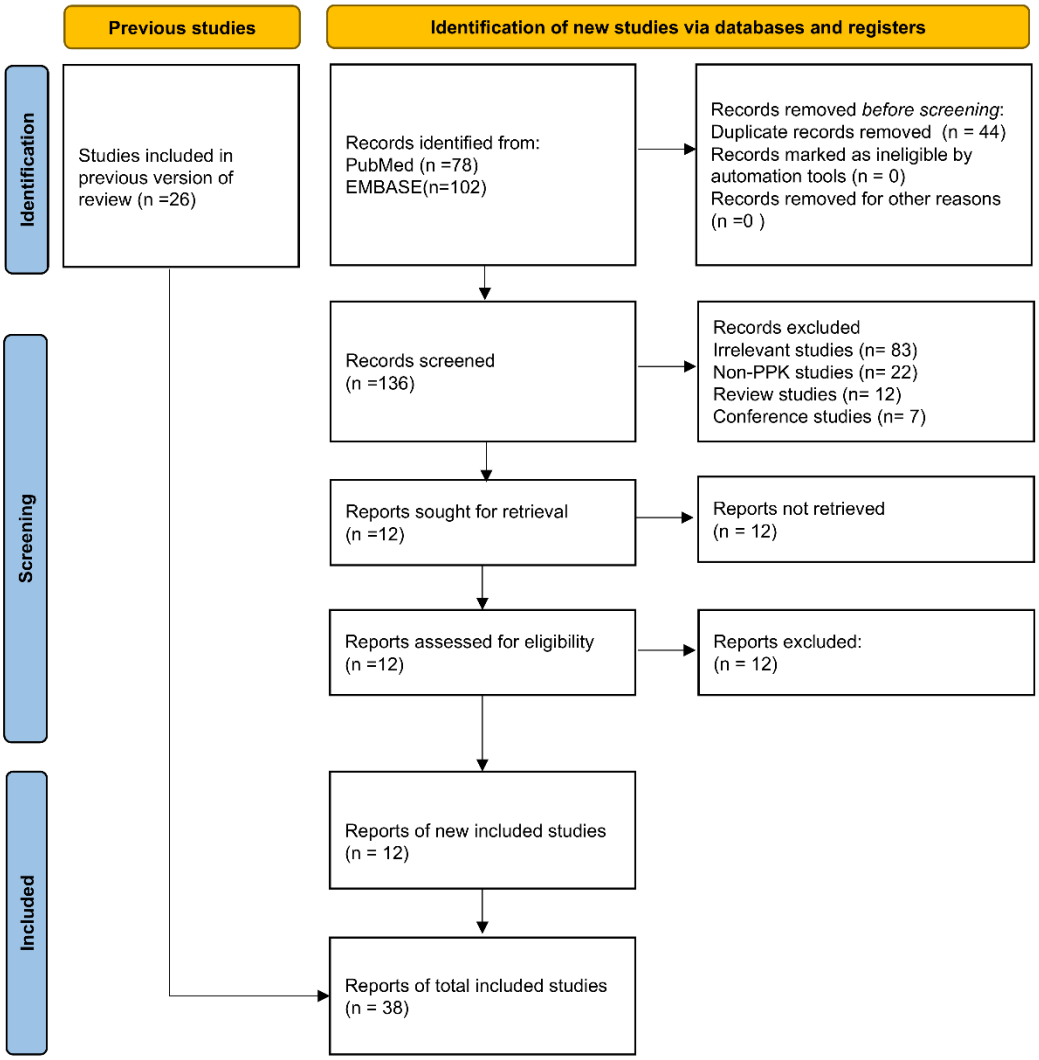
PRISMA flow diagram for identifying population pharmacokinetic studies of oxcarbazepine



PRISMA flow diagram for identifying population pharmacokinetic studies of topiramate



PRISMA flow diagram for identifying population pharmacokinetic studies of valproic acid



Appendix 2. The new identification of population pharmacokinetic studies.

The PPK models of other 4 ASMs were not identified in previous study, including brivaracetam, lacosamide, perampanel and vigabatrin. Therefore, the PPK studies of these ASMs were screened in the PubMed and Embase from inception until 30 November, 2024.

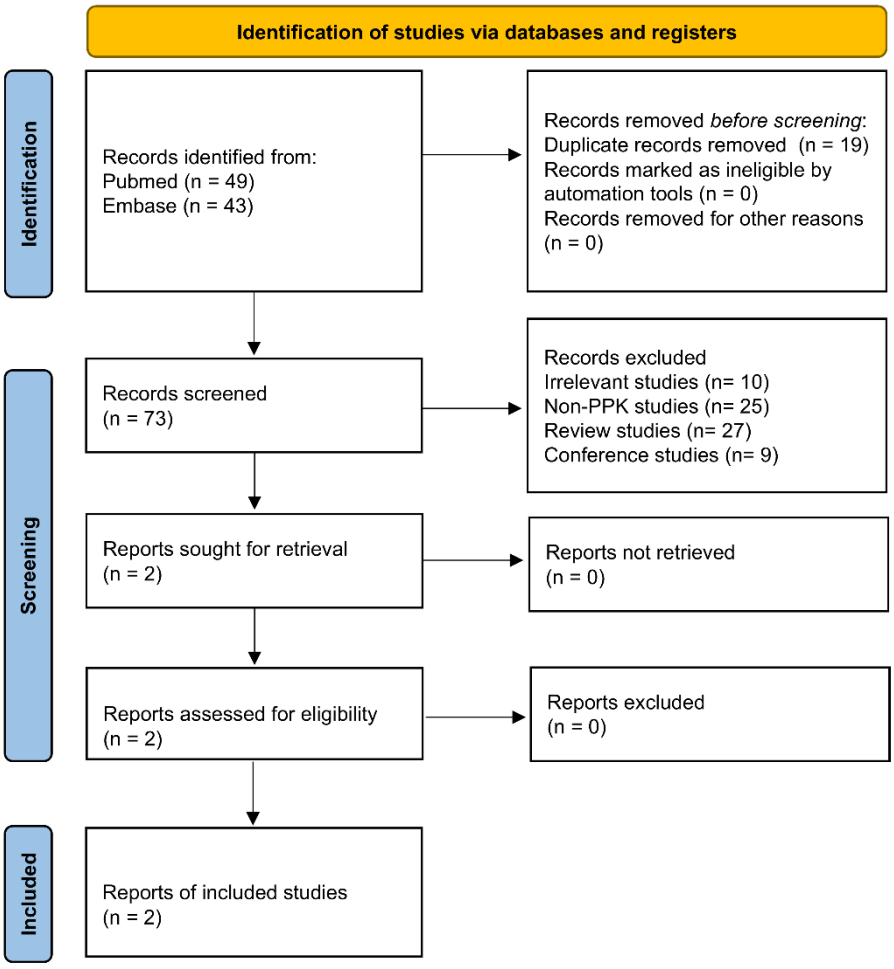
A study was considered eligible for inclusion if it met the following criteria: (1) the study population included patients with epilepsy; (2) the study was focused on population PKs or pharmacokinetic/pharmacodynamic (PK/PD) analysis; (3) the study enrolled more than 30 participates; (4) the concentration-time profiles of typical patients based on the established model showed no obvious deviation from the others.

A study was excluded if: (1) it was a review or only focused on the methodology, algorithm, or software considerations; (2) it was published in a non-English language; (3) the information on methodology or pharmacokinetics was insufficient; (4) only injection formulation was used; and (5) only neonates were enrolled.

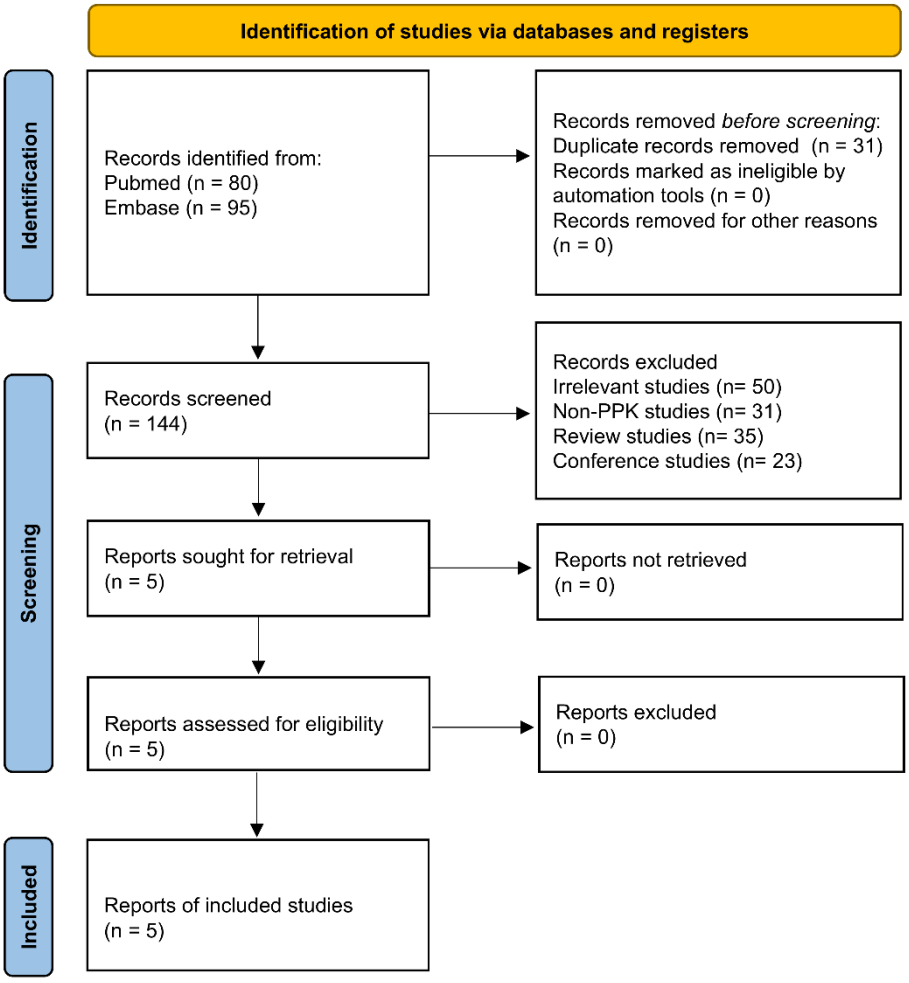
When several studies were identified for one ASM, preference was given to studies that prospectively investigated in multi-centers or studies that included intensive samplings. This process was also performed by two independent reviewers. Moreover, a third senior investigator was consulted to resolve the discrepancies.

The PRISMA flow diagram for the identification of PPK studies of brivaracetam, lacosamide, perampanel and vigabatrin were shown below.

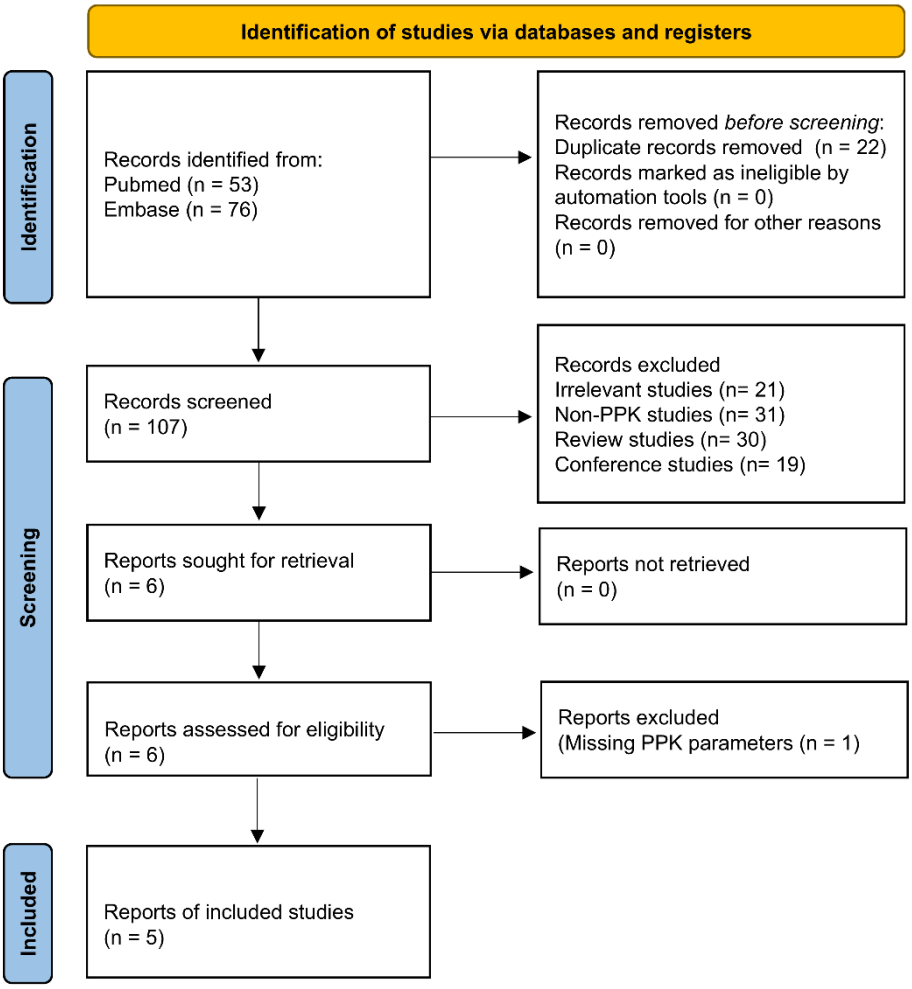
PRISMA flow diagram for identifying population pharmacokinetic studies of brivaracetam



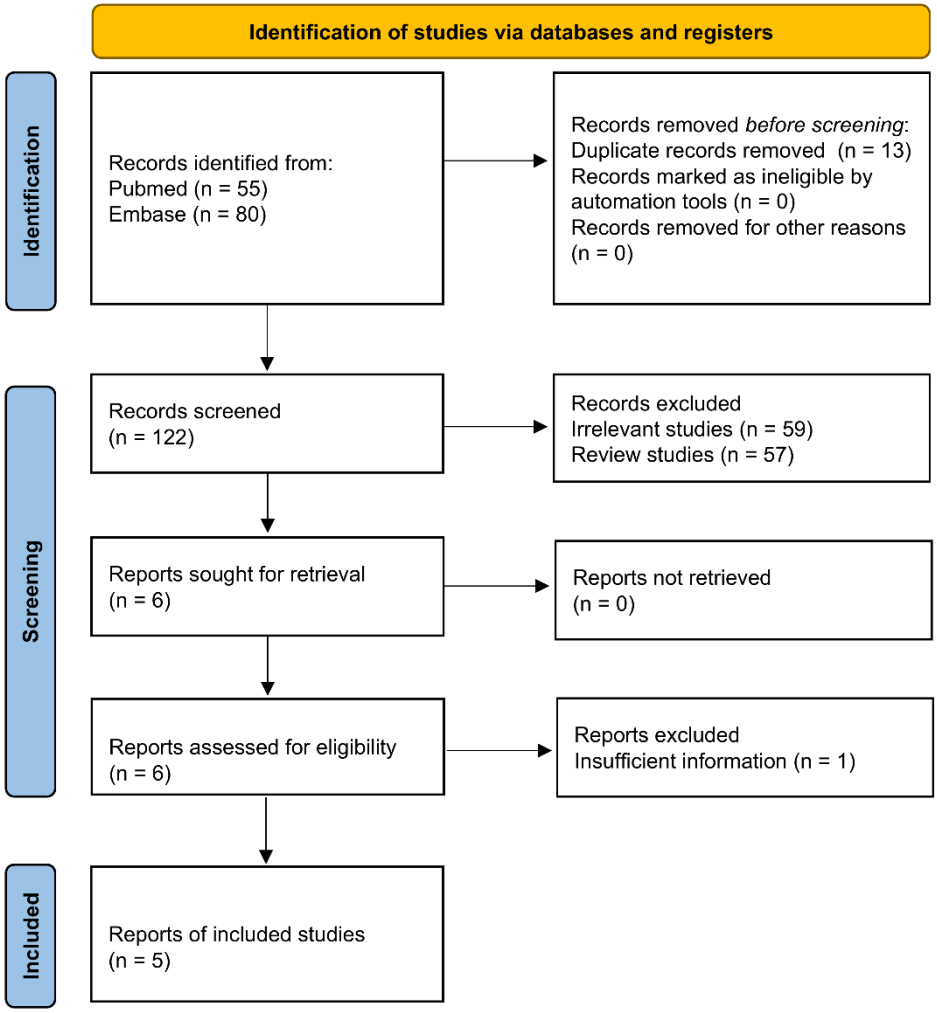
PRISMA flow diagram for identifying population pharmacokinetic studies of lacosamide



PRISMA flow diagram for identifying population pharmacokinetic studies of perampanel



PRISMA flow diagram for identifying population pharmacokinetic studies of Vigabitrin



Appendix 3. The identified population pharmacokinetic studies of antiseizure medications and corresponding dosing regimens.

Drug	Population	Model (year)	Dosing regimens
Brivaracetam	Children	Schomaker et al. (2017)[2]	25 mg q12h
	Adult	Schomaker et al. (2016)[3]	50 mg q12h
Carbamazepine	Children	Jiao et al. (2004)[4]	100 mg q12h
	Adult		400 mg q12h
Clobazam	Children	Saruwatari et al. (2014)[5]	5 mg q12h
	Adult		10 mg q12h
Eslicarbazepine acetate	Children	Sunkaraneri et al. (2018)[6]	400 mg q24h
	Adult	Gidal et al. (2018)[7]	800 mg q24h
Lacosamide	Children	Winkler et al. (2019)[8]	100 mg q12h
	Adult	Winkler et al. (2019)[9]	150 mg q12h
Lamotrigine	Children	van Dijkman et al. (2018)[10]	50 mg q12h
	Adult		100 mg q12h
	Pregnant women	Wang et al. (2021)[11]	100 mg q12h
Levetiracetam	Children	Chhun et al. (2009)[12]	250 mg q12h
	Adult	Pigeolet et al. (2007)[13]	500 mg q12h
	Pregnant women	Li et al. (2023)[14]	500 mg q12h
Oxcarbazepine	Children	Lin et al. (2019)[15]	300 mg q12h
	Adult	Lin et al. (2019)[16]	600 mg q12h
Perampanel	Children	Li et al. (2024)[17]	4 mg q12h
	Adult	Takenaka et al. (2018)[18]	8 mg q12h
Phenobarbital	Children	Goto et al. (2007)[19]	60 mg q12h
	Adult		60 mg q12h
Topiramate	Children	Girgisz et al. (2010)[20]	100 mg q12h
	Adult		200 mg q12h
Valproic acid	Children	Ding et al. (2015)[21]	250 mg q12h
	Adult	Teixeira-da-Silva et al. (2022)[22]	500 mg q12h
Vigabatrin	Children	Nielsen et al. (2014)[23]	1000 mg q24h
	Adult		1500 mg q24h
Zonisamide	Children	Okada et al. (2008)[24]	50 mg q12h
	Adult		200 mg q12h

Children: 8 years old, 25 kg, 127 cm, eGFR 90 mL/min; adult: 40 years old, 70 kg, 180 cm, eGFR 90 mL/min; pregnant women, 25 years old, 70 kg, 160 cm, eGFR 90 mL/min, 30 weeks pregnant.

Appendix 4. Population pharmacokinetic parameter estimates of the identified ASMs studies.

Drug (population)	Study (Publication year)		Fixed effect parameters	BSV (%)	RUV
Brivaracetam (Children)	Schoemaker et al. (2017) [2]	*Ka*	=1.84	31.9	23.4%
		CL[(a)]	$=3.63\times(LBW/70)^{0.75}\times 1.479^{CBZ}\times 1.408^{PB}\times 0.899^{VPA}$	22.8	
		V	=47.8×(LBW/50)	16.7	
Brivaracetam (Adults)	Schoemaker et al. (2016) [3]	*Ka*	=1.42	101.2	20.7%
		CL	$=3.63\times(WT/70)^{0.565}\times 1.348^{CBZ}\times 1.268^{PHT}\times 1.239^{PB}$	24.7	
		V	$=48.1\times(WT/70)^{0.639}$	30.5	
Carbamazepine (Children & Adults)	Jiao et al. (2004) [4]	*Ka*	= 1.2	/	14.46%
		CL	$= 0.141\times DD^{0.406}\times WT^{0.117}\times 1.23^{VPA}\times 1.44^{PHT}\times 1.26^{PB}$	10.3	0.454 mg/L
		V	= 72	42.9	
Clobazam (Children & Adults)	Saruwatari et al. (2014) [5]	*Ka*	= 0.0594	/	32.7 %
		CL[(b)]	$= 0.347\times WT^{0.54}\times 0.484^{ZNS}\times 1.66^{PB}\times 1.93^{PHT}$	81.8	
		V	$= 13.3\times WT^{0.136}$	/	
Eselicazepine acetate (Children)	Sunkaraneni et al. (2018) [6]	*Ka*	= 0.895 (tablet) = 4.18 (oral suspension)	83.8 /	23.3 %
		CL	$= 1.69\times(WT/33)^{0.75}\times(1 - 0.176\times LEV)\times(1 + 0.6626\times PB)$	25	
		V	= 32.8 × WT/33	13.2	
Eselicazepine acetate (Adults)	Gidal et al. (2018) [7]	*Ka*	= 2.34	126.49	11.1%
		CL	$= (2.43 + 1.08\times(DCBZ/800)^{0.411} + 1.24\times PBL + 0.0132\times(WT - 70))\times(eGFR/115.7)^{0.195}$	27.04	2.3 mg/L
		V	$= (61.3 - 9.9\times SEXF + 12\times PBL)\times(WT/70)^{0.617}$	17.69	
Lacosamide (Children)	Winkler et al. (2019) [8]	*Ka*	=2.45	55.1	Not reported
		CL	$=2.37\times(WT/70)^{0.624}\times 1.535^{IND}$	32.3	
		V	=50.6×(WT/70)	24	

Appendix 4. continued

Drug (population)	Study (Publication year)		Fixed effect parameters	BSV (%)	RUV
Lacosamide (Adults)	Winkler et al. (2019) [9]	*Ka*	=4.05	70.9	50%
		CL	$=2.57\times(WT/70)^{0.75}\times 1.50^{CBZ} \times 2.59^{PB}\times 1.56^{PHT}$	23.0	
		V_c	$=28.2\times(WT/70)^{0.722}$	35.6	
		V_p	=13.1	55.0	
		Q	=39.1	/	
		F	=1.01	3.8	
		D1	=0.401	58.0	
Lamotrigine (Adult & Children)	Van Dijkman et al. (2018)[10]	*Ka*	= 2.43 (immediate-release formulation) = 0.087 (extended-release formulation)	60.9 (immediate-release formulation) 46(extended-release formulation)	15.6% 0.236 mg/L
		CL[(c)]	$= 2.23 \times(WT/70)^{0.75} \times 1.765^{CBZ} \times 2.29^{PHT} \times 0.526^{VPA}$ $= 2.23 \times(WT/70)^{0.75} \times 1.765^{CBZ} \times 2.29^{PHT} \times 0.526^{VPA} \times 0.852$ (if >65 years)	27.4%	
		V	$= 1.97 \times(WT/70)^{0.75}$	62.6%	
Lamotrigine (Pregnant women)	Wang et al. (2021)[11]	*Ka*	= 1.93	/	30.6 % 0.032 mg/L
		CL	$= 3.30 \times \left(\frac{GA}{9}\right)^{0.347} \times (1 - 0.507 \times INH)$	37.7	
		V	= 68.8	/	

Appendix 4. continued

Drug (population)	Study (Publication year)		Fixed effect parameters	BSV (%)	RUV
Levetiracetam (Children)	Chhun et al. (2009) [12]	*Ka*	= 3.83	117	18.90 %
		Tlag	= 0.283	COR=16.7	
		CL	$= 2.47 \times (WT/33)^{0.89}$	24.3	
		V	$= 21.9 \times (WT/33)^{0.93}$	16.3	
Levetiracetam (Adults)	Pigeolet et al. (2007) [13]	*Ka*	= 2.44 (fed) = 4.80 (fasted)	108	27.5 %
		CL	$= 4.02 \times (WT/70)^{0.268} \times (eGFR/110)^{0.122} \times 0.896^{SEXF} \times 1.09^{IND} \times 0.812^{VPA}$	19.5	
		V	$= 52.7 \times (WT/70)^{0.952}$	11.8	
Levetiracetam (Pregnant women)	Li et al. (2023)[14]	K_a	= 2.44	/	36.1%
		CL	$= 3.82 \times (WT/65)^{0.939}$ × 1.22 (if pregnant 14~28 weeks) × 1.15 (if pregnant >28 weeks)	18.9	
		V	= 42	/	
Oxcarbazepine (Children)	Lin et al. (2019) [15]	*Ka*	= 0.83	11.1	2.992 mg/L
		CL	$= 1.68 \times (WT/70)^{(0.624 - (0.233 \times WT^{219})/(8.97^{219} + WT^{219}))}$		
		V	= 14.7		
Oxcarbazepine (Adults)	Lin et al. (2019) [16]	*Ka*	= 0.46	/	24.5 %
		CL	$= 2 \times (WT/70)^{0.46} \times (eGFR/80)^{0.741}$	12.7	
		V	= 102	58.7	
Perampanel (Children)	Li et al. (2024) [17]	*Ka*	= 1.19	/	17.25%
		CL	$= 0.59 \times (WT/70)^{0.51} \times (TBIL/5.9)^{-0.24} \times 1.53^{OXC}$	44.7	
		V	$= 97.27 \times (WT/70)$	97.5	

Appendix 4. continued

Drug (Age group)	Study (Publication year)		Fixed effect parameters	BSV (%)	RUV
Perampanel (Adults)	Takenaka et al. (2017) [18]	*Ka* (d)	= 1.19	/	8.72%
		CL(e)	= $0.668 \times (ALT/17)^{-0.0901} \times 0.822^{SEXF} \times 0.908^{Asian} \times 2.95^{CBZ} \times 1.99^{OXC/PHT} \times 1.21^{TOP/PB}$	43.5	
		V	= 43.5	51.5	
Phenobarbital (Children & Adults)	Goto et al. (2007) [19]	*Ka*	= 2	/	3.49 mg/L
		CL (b)	= $0.223 \times (WT/40)^{0.21} \times 0.68^{VPA} \times 0.85^{PHT}$	17.3	
		V	= 14.78	171.2	
Topiramate (Children & Adults)	Girgis et al. (2010) [20]	*Ka*	= 0.105	22.34	25.46 % 0.1797 mg/L
		K_{23}	= 0.577	/	
		K_{32}	= 0.0586	/	
		CL	= $1.21 \times (WT/69.9)^{0.453} \times e^{(-0.00306 \times (Age - 31.4))} \times 0.686^{VPA} \times 1.94^{IND}$	27.28	
		V	= $4.61 \times (WT/69.9)^{1.14}$	116.2	
Valproic acid (Children)	Ding et al. (2015) [21]	*Ka*	= 2.64 (syrup) = 1.57 (tablet)	/	13.3 mg/L
		CL	= $0.3 \times 1.43^{CBZ} \times (WT/70)^{(0.791 - 0.096 \times Age^{8.63}/(0.802^{8.63} + Age^{8.63}))} \times (1 + 2.8 \times DD^{1.68}/(37.4^{1.68} + DD^{1.68}))$	19.5%	
		V	= $22.2 \times (WT/70)$	/	
Valproic acid (Adults)	Teixeira-da-Silva et al. (2022) [22]	*Ka* (g)	= 2.64 (oral solution) = 0.78 (gastro-resistant tablets) = 0.38 (modified-release coated tablets)	/	8.5 mg/L
		CL	= $0.1 \times (WT/60)^{0.7} \times DD^{0.2} \times 1.36^{CBZ} \times 1.25^{PHT} \times 1.11^{PB}$	18	
		V	= $0.14 \times WT$	/	

Appendix 4. continued

Drug (Age group)	Study (Publication year)		Fixed effect parameters	BSV (%)	RUV
Vigabatrin (Children & Adult)	Nielsen et al. (2014) [23] (h)	CL	$=6.52\times(eGFR/100)^{0.538}\times0.525$ (for children aged 3-16 years)	/	93.3% (i)
		V_c	$= 23.9 \times (WT/70)^{0.406}$	18.2%	
		k	$=CL/V_c$	14.5%	
		V_p	$= 32.3 \times (WT/70)^{1.03}$	/	
		Q	$= 3.59 \times (WT/70)^{0.692}$	/	
		ktr	$= 11.4 \times (Age/28)^{0.3}$	22.9%	
		F	= 1	/	
		n	= 5	/	
Zonisamide (Children & Adults)	Okada et al. (2008) [24]	*Ka*	= 2	/	22.4 %
		CL (b)	$= 1.065 \times (WT/44)^{0.77} \times DD^{-0.17} \times 1.24^{CBZ} \times 1.28^{PHT} \times 1.29^{PB}$	27.6	
		V	$= 1.23 \times WT$	/	

ALT Alanine Aminotransferase (IU/L); *AGE* age of patients (year); *CBZ* carbamazepine; *CL* apparent clearance (L/h); *COR* covariance between CL and V; *D1* duration for zero-order absorption (h); *DCBZ* Carbamazepine daily dose (mg); *DD* daily dose (mg/day); *eGFR* estimated glomerular filtration rate (mL/min/1.73m^2), *F* absorption rate; *GA* gestational age (weeks); *IND* enzyme-inducing antiepileptic drugs; *k* elimination rate constant (h^{-1}); K_a absorption rate constant (h^{-1}); *KM* Michaelis constant; K_{23} inter-compartment rate constants from central to peripheral compartment (h^{-1}); K_{32} inter-compartment rate constants from peripheral to central compartment (h^{-1}); *ktr* transit rate constant (h^{-1}); *LBW* lean body weight (kg); *LEV* levetiracetam; *n* number of transit compartments; *OXC* oxcarbazepine; *PB* phenobarbital; *PBL* Phenobarbital-like AEDs including phenytoin and primidone; *PHT* phenytoin; *Q* inter-compartment clearance between the central and peripheral compartment; *SEXF* 1 for female and 0 for male; *TBIL* total bilirubin; *Tlag* absorption lag time (h); *TOP* topiramate; *V* apparent volume of distribution (L); V_c apparent volume of distribution of the central compartment (L); *VM* maximum reaction velocity; V_p apparent volume of distribution of the peripheral compartment (L); *VPA* valproate acid; *WT* body weight (kg); *ZNS* zonisamide.

(a) For males: $LBW=1.1\times WT-0.0128\times(WT/HT/100)^2$, for females: $LBW=1.07\times WT-0.0148\times(WT/HT/100)^2$, where WT is weight (kg), HT is height (cm).

(b) The original equation contains the effect of genotype, and the equation used in the dashboard has been normalized according to gene frequency reported in the original literature.

(c) CL for patients aged <2 years is not included in the dashboard.

(d) The *Ka* was fixed from another study conducted in children [17].

(e) Asian=0, if Japanese, Chinese and non-Asian; Asian=1, if Asians except for Japanese and Chinese. In the dashboard, the CL for Japanese, Chinese and non-Asian

was defaulted.

(f) The *Ka* was fixed from another study conducted in healthy volunteers [25].

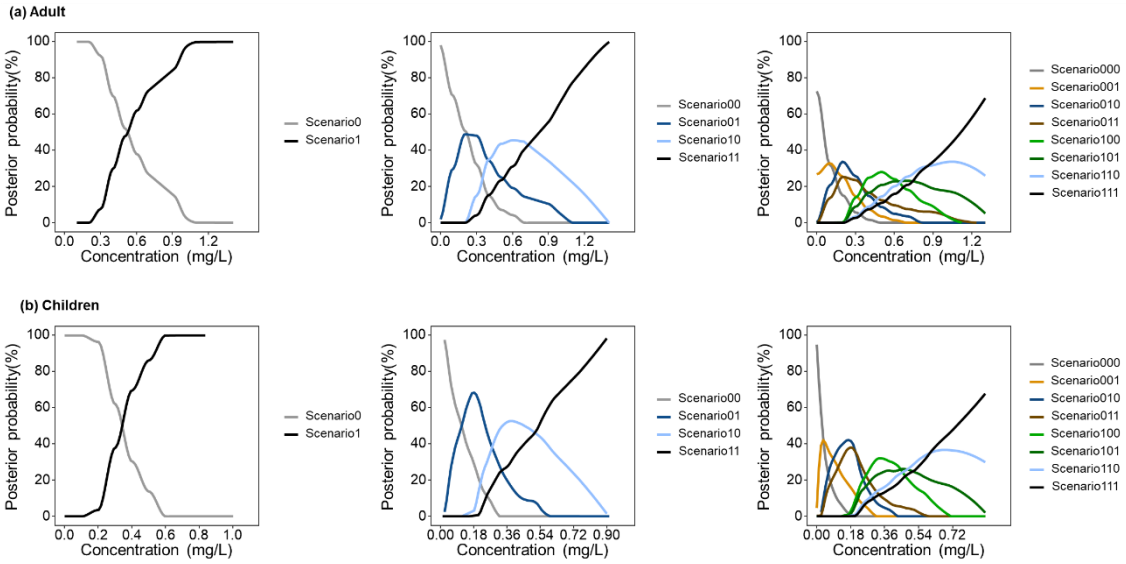
(g) In the dashboard, absorption rate for modified-release coated tablets was applied.

(h) The model is simplified as a two-compartment model with first-order absorption and elimination when developing the dashboard to shorten the calculation time.

(i) The residual unexplained variability in study 118 was applied.

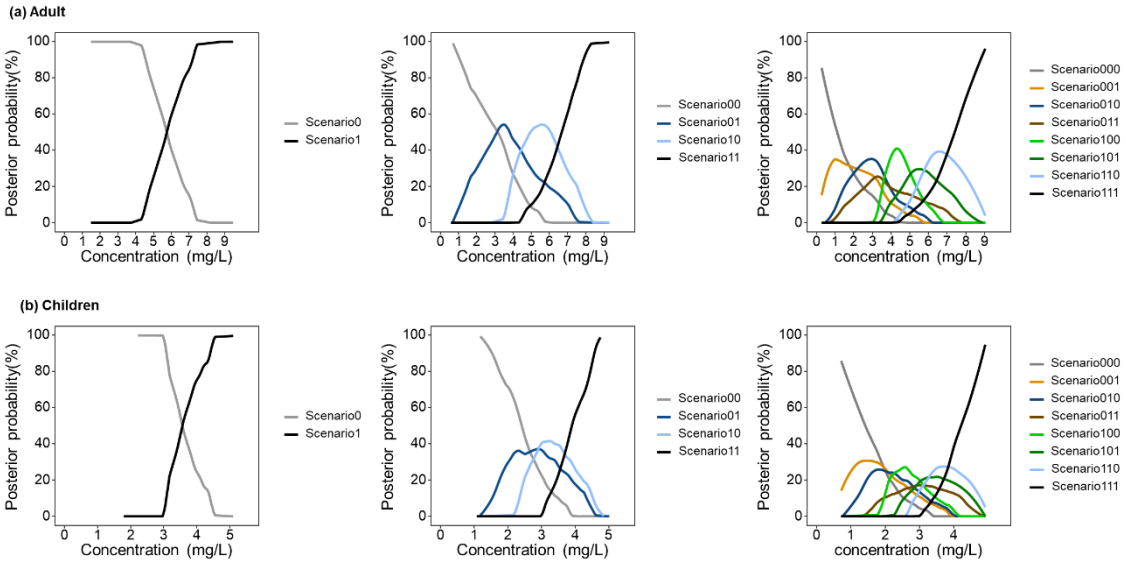
Appendix 5. The posterior probabilities-concentration curves of brivaracetam.

(a) Adult: 40 years, 70 kg, 180 cm, taking brivaracetam 50 mg q12h; (b) children: 8 years, 25 kg, 127cm, taking brivaracetam 25 mg q12h.



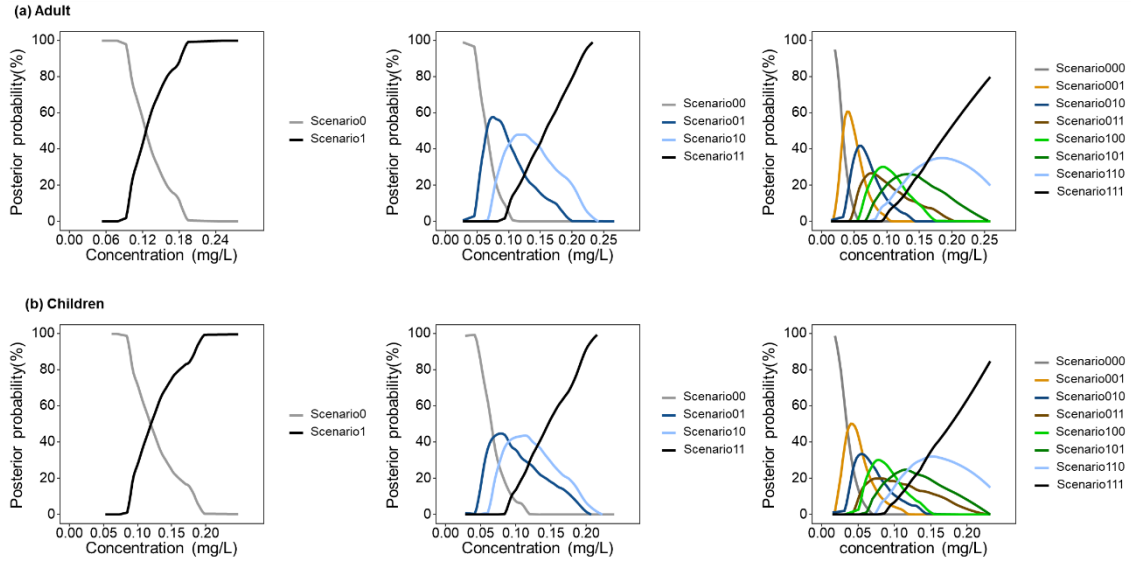
Appendix 6. The posterior probabilities-concentration curves of carbamazepine.

Adult: 40 years, 70 kg, 180 cm, taking carbamazepine 400 mg q12h; children: 8 years, 25 kg, 127cm, taking carbamazepine 100 mg q12h.



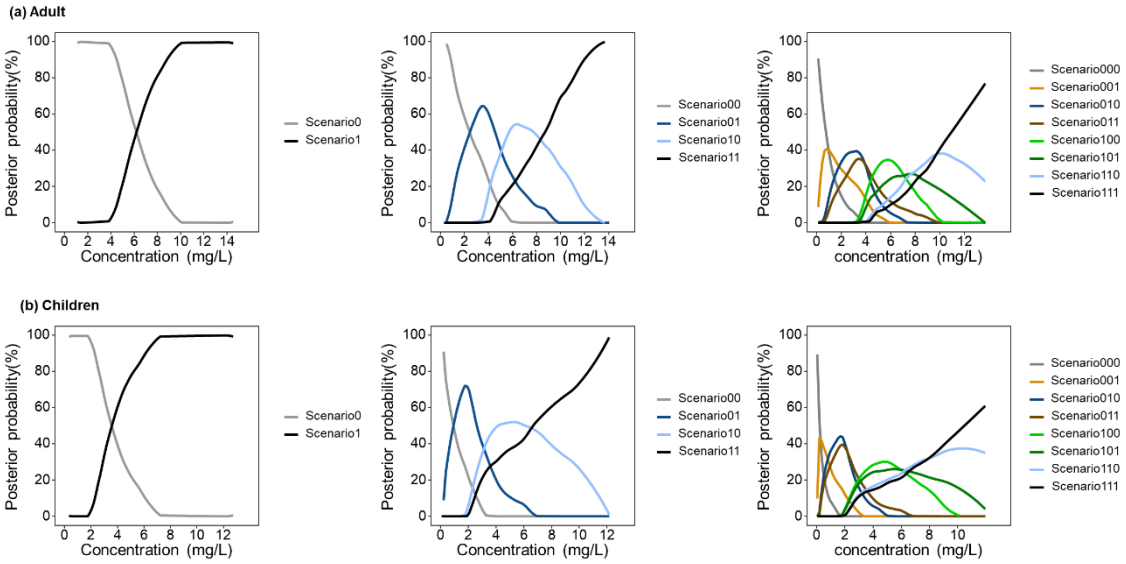
Appendix 7. The posterior probabilities-concentration curves of clobazam.

Adult: 40 years, 70 kg, 180 cm, taking clobazam 10 mg q12h; children: 8 years, 25 kg, 127cm, taking clobazam 5 mg q12h.



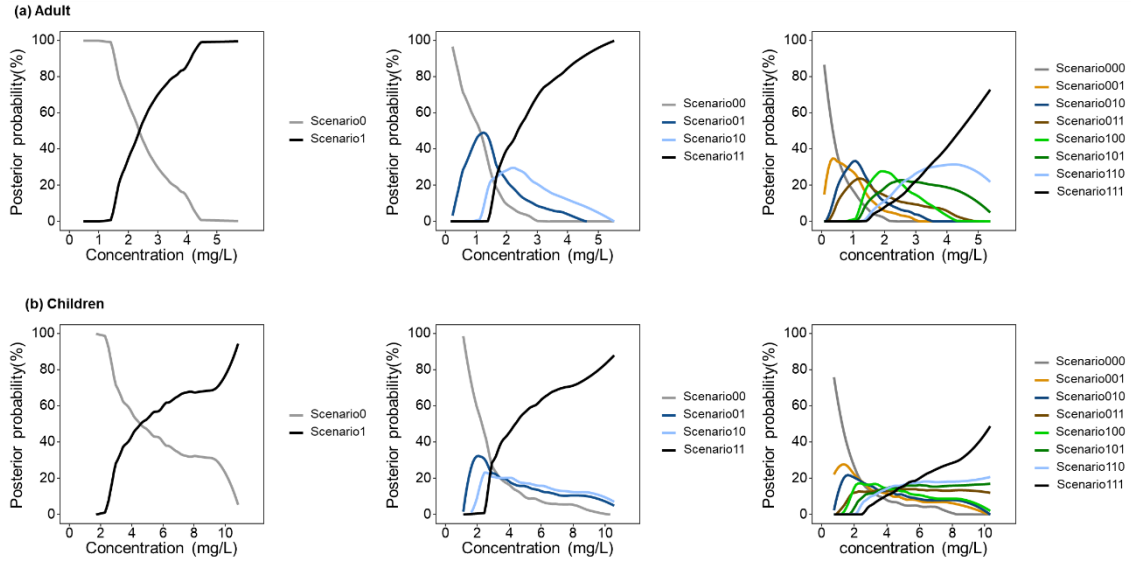
Appendix 8. The posterior probabilities-concentration curves of eslicarbazepine acetate.

Adult: 40 years, 70 kg, 180 cm, taking eslicarbazepine acetate tablet 800 mg q24h; children: 8 years, 25 kg, 127cm, taking eslicarbazepine acetate tablet 400 mg q24h.



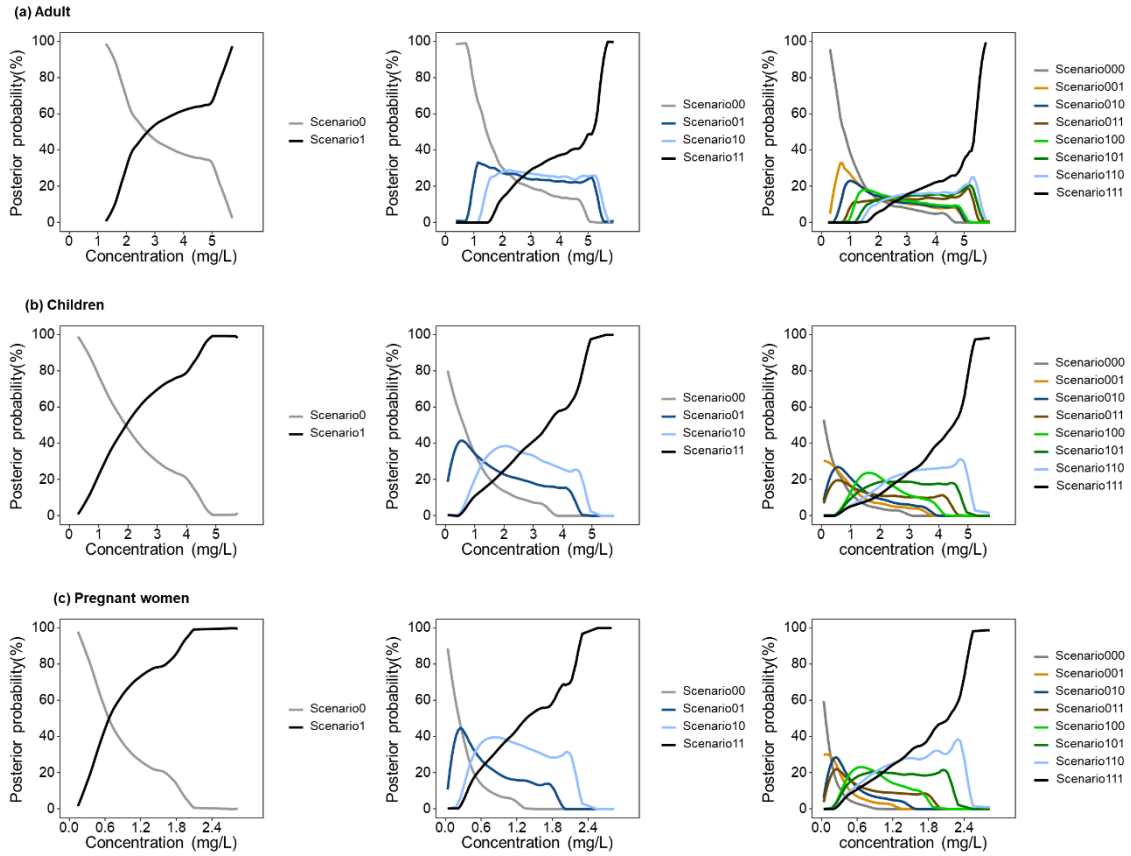
Appendix 9. The posterior probabilities-concentration curves of lacosamide.

Adult: 40 years, 70 kg, 180 cm, taking lacosamide 150 mg q12h; children: 8 years, 25 kg, 127cm, taking lacosamide 100 mg q12h.



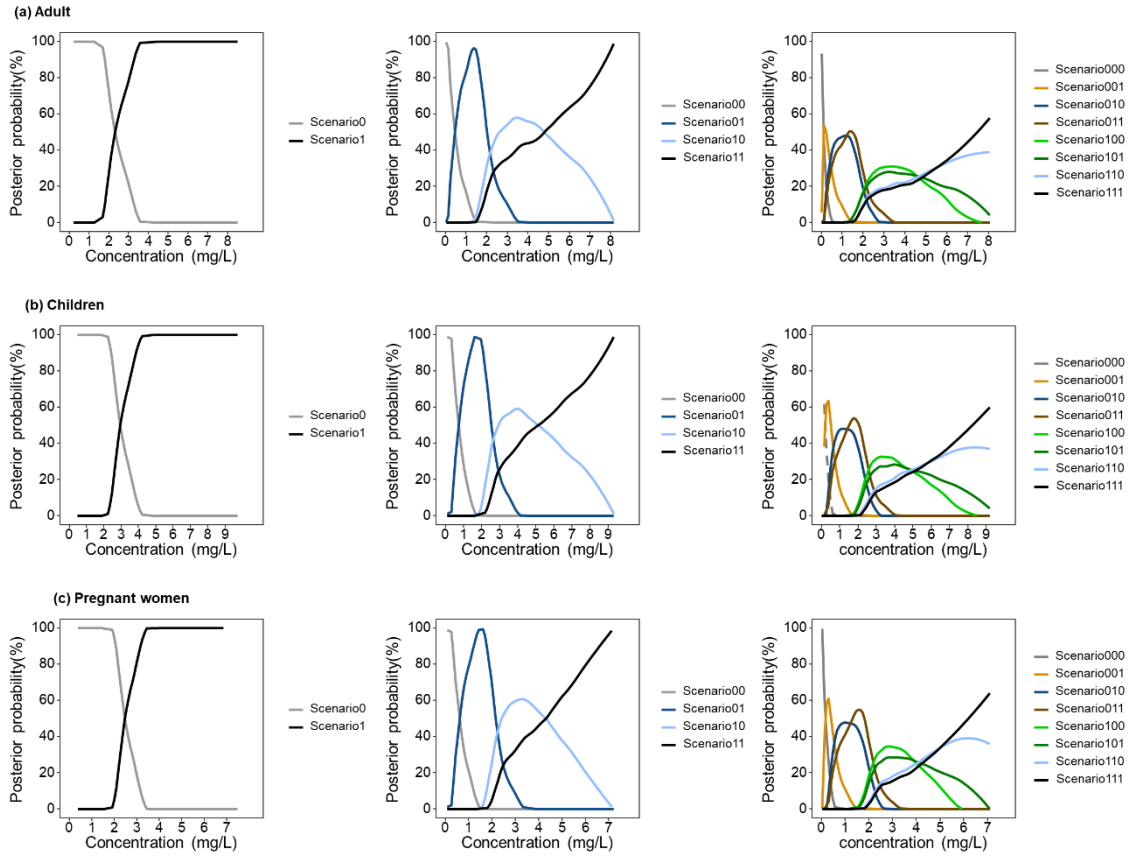
Appendix 10. The posterior probabilities-concentration curves of lamotrigine.

Adult: 40 years, 70 kg, 180 cm, taking lamotrigine 100 mg q12h; children: 8 years, 25 kg, 127cm, taking lamotrigine 50 mg q12h; pregnant women, 25 years, 70 kg, 160 cm, being 30 weeks pregnant, taking lamotrigine 100 mg q12h.



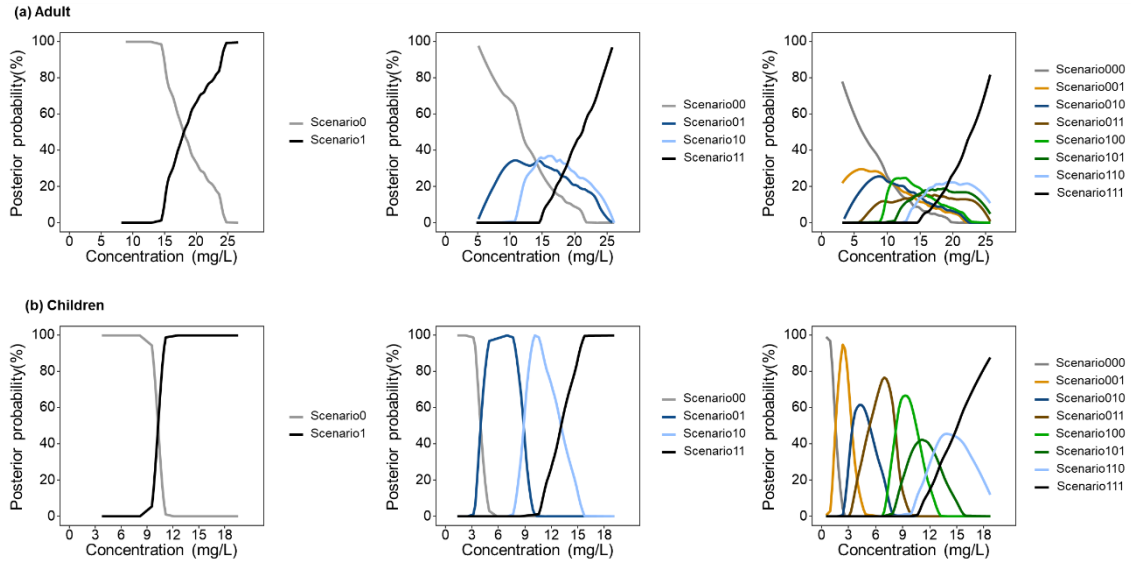
Appendix 11. The posterior probabilities-concentration curves of levetiracetam.

Adult: 40 years, 70 kg, 180 cm, taking levetiracetam 500 mg q12h; children: 8 years, 25 kg, 127cm, taking levetiracetam 250 mg q12h; pregnant women, 25 years, 70 kg, 160 cm, being 30 weeks pregnant, taking levetiracetam 500 mg q12h.



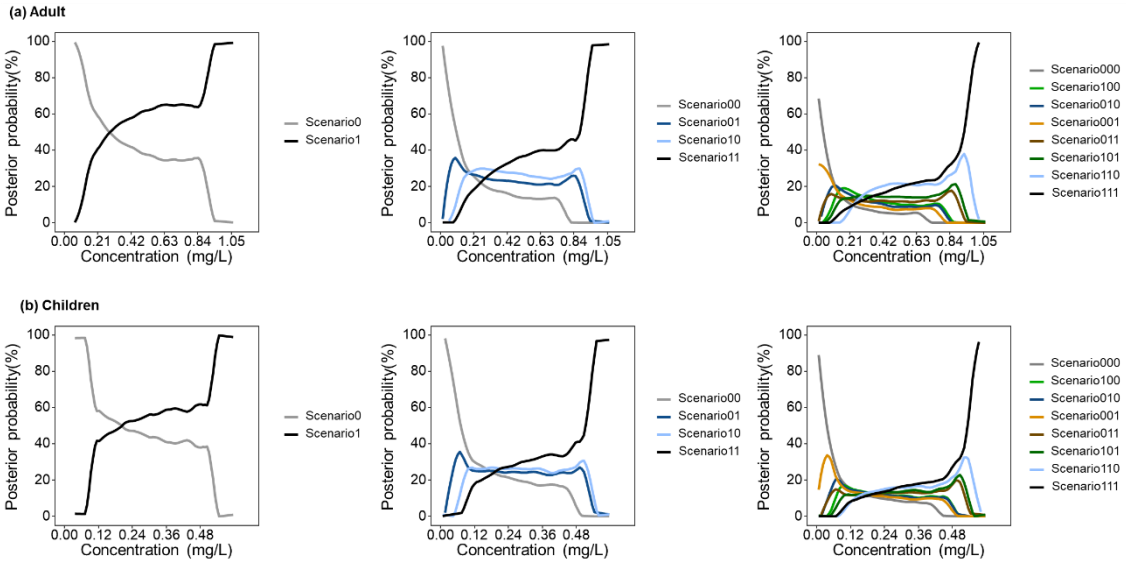
Appendix 12. The posterior probabilities-concentration curves of oxcarbazepine.

Adult: 40 years, 70 kg, 180 cm, taking oxcarbazepine 600 mg q12h; children: 8 years, 25 kg, 127cm, taking oxcarbazepine 300 mg q12h.



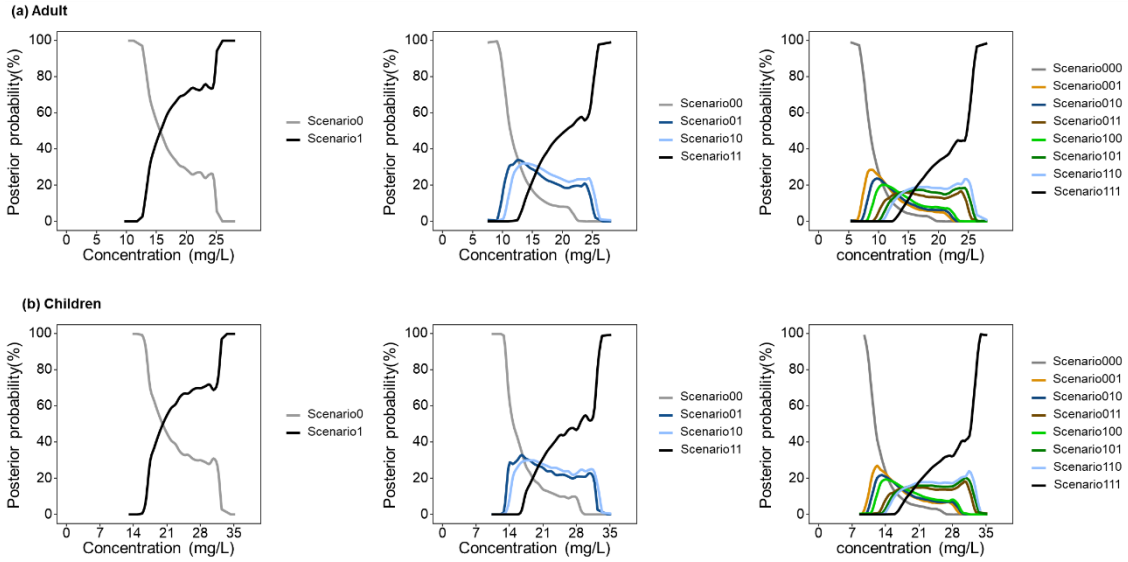
Appendix 13. The posterior probabilities-concentration curves of perampanel.

Adult: 40 years, 70 kg, 180 cm, taking perampanel 8 mg q24h; children: 8 years, 25 kg, 127cm, taking perampanel 4 mg q24h.



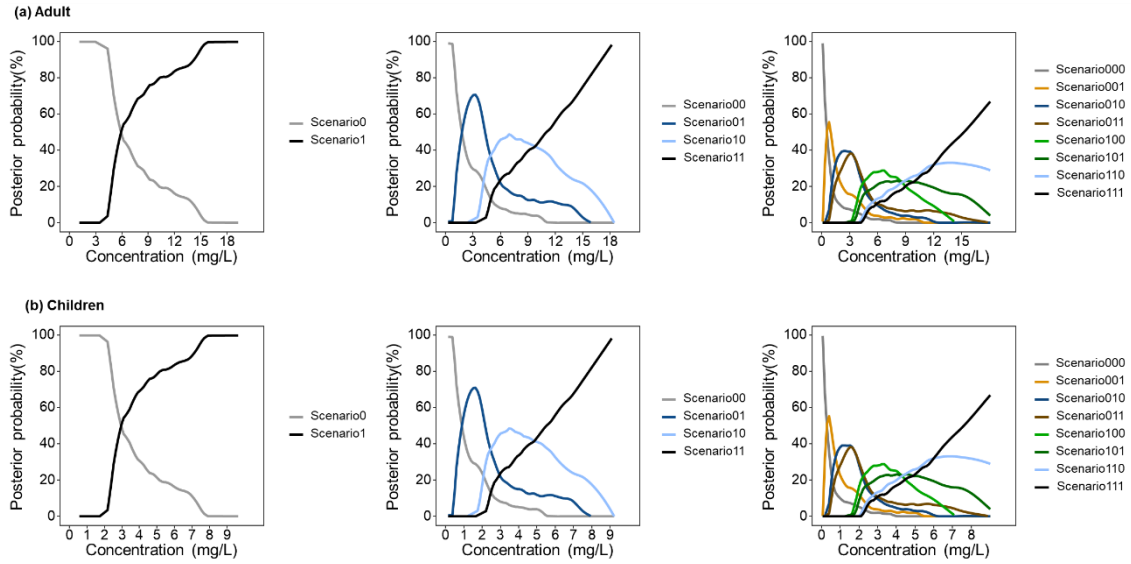
Appendix 14. The posterior probabilities-concentration curves of phenobarbital.

Adult: 40 years, 70 kg, 180 cm, taking phenobarbital 60 mg q12h; children: 8 years, 25 kg, 127cm, taking phenobarbital 60 mg q12h.



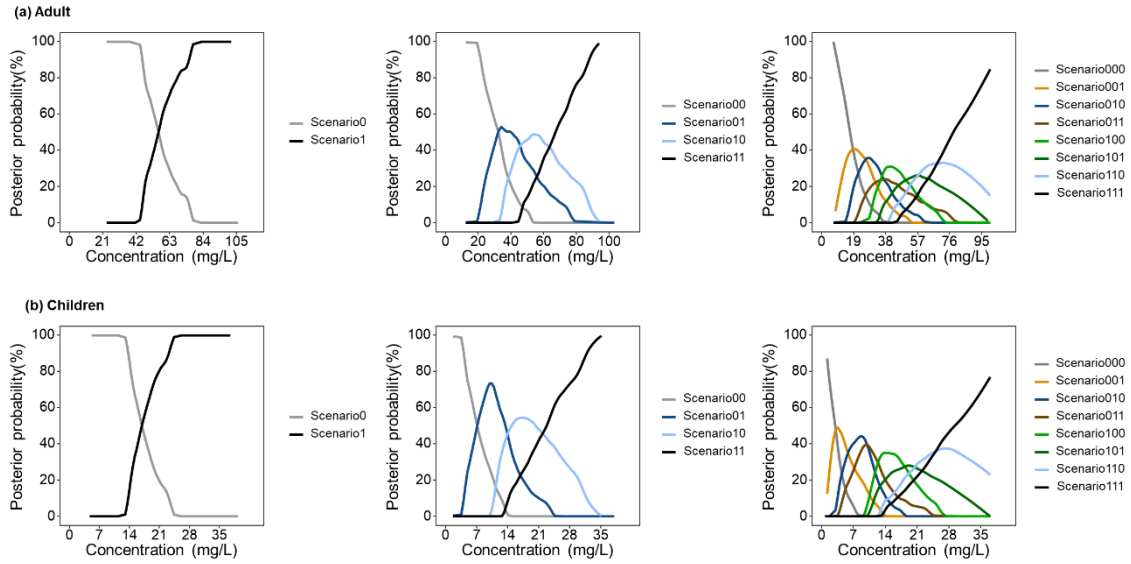
Appendix 15. The posterior probabilities-concentration curves of topiramate.

Adult: 40 years, 70 kg, 180 cm, taking topiramate 200 mg q12h; children: 8 years, 25 kg, 127cm, taking topiramate 100 mg q12h.



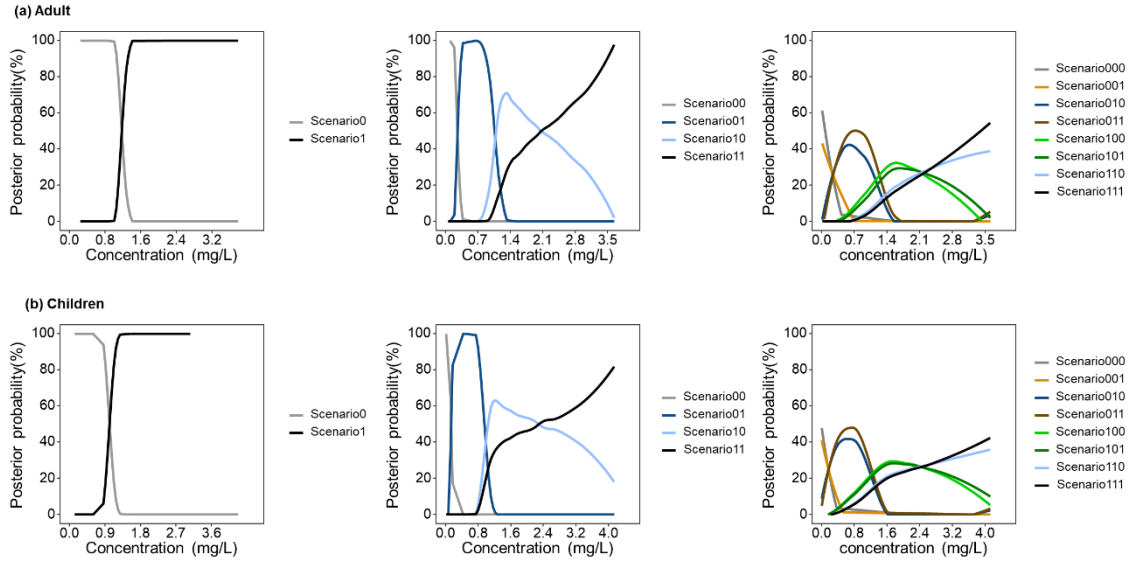
Appendix 16. The posterior probabilities-concentration curves of valproic acid.

Adult: 40 years, 70 kg, 180 cm, taking valproic acid 500 mg q12h; children: 8 years, 25 kg, 127cm, taking valproic acid 250 mg q12h.



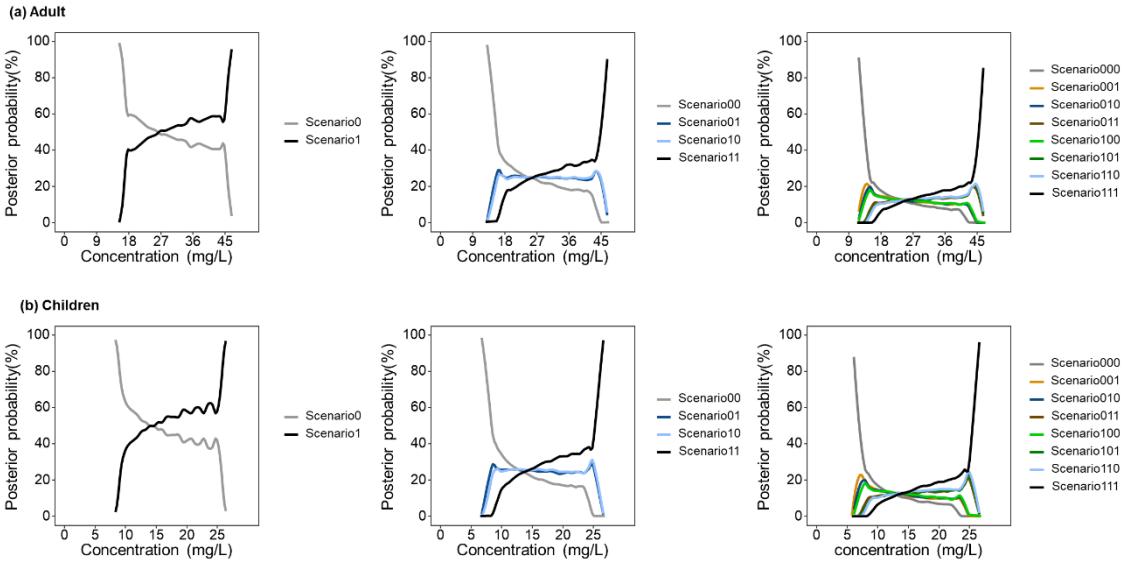
Appendix 17. The posterior probabilities-concentration curves of vigabatrin.

Adult: 40 years, 70 kg, 180 cm, taking vigabatrin 1500 mg q24h; children: 8 years, 25 kg, 127cm, taking vigabatrin 1000 mg q24h.



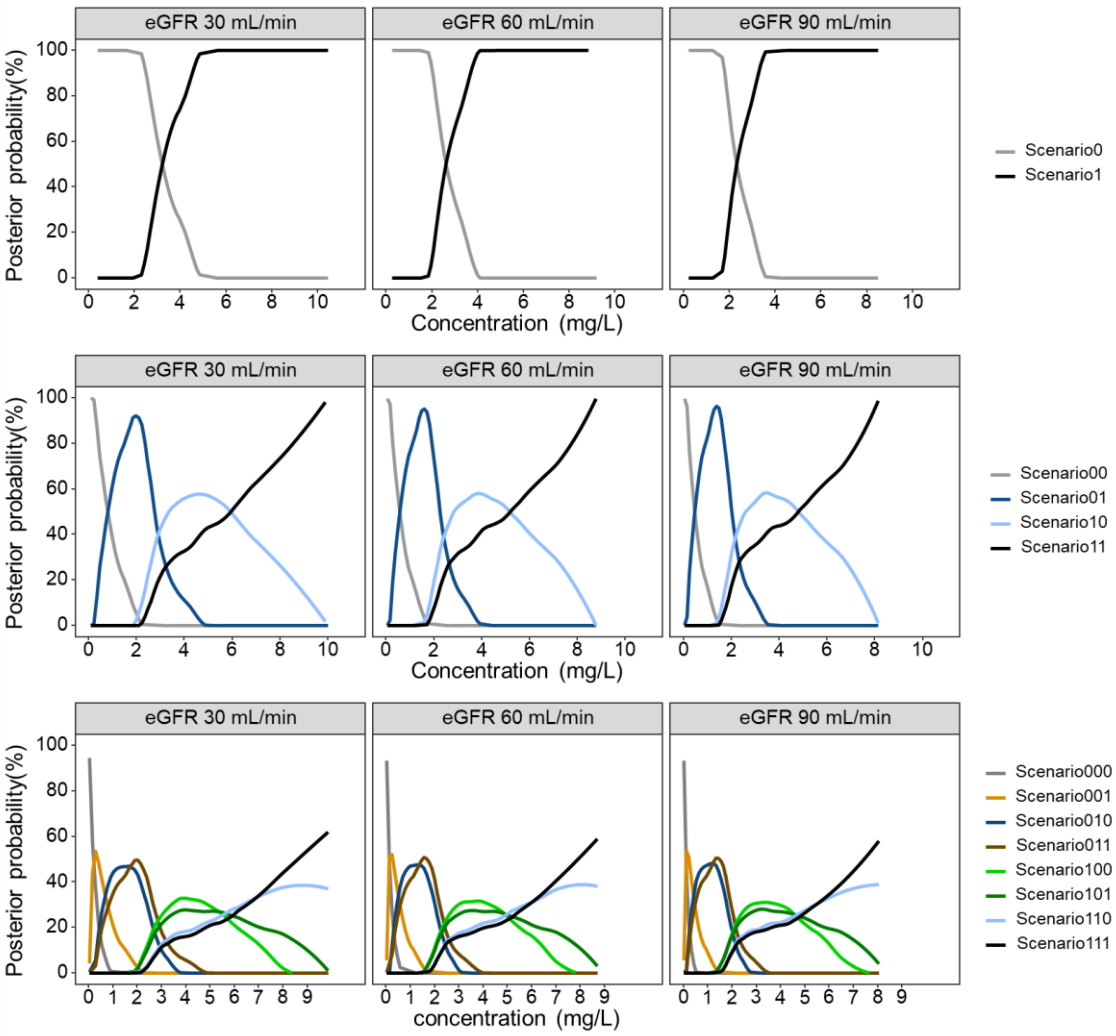
Appendix 18. The posterior probabilities-concentration curves of zonisamide.

Adult: 40 years, 70 kg, 180 cm, taking zonisamide 200 mg q12h; children: 8 years, 25 kg, 127cm, taking zonisamide 50 mg q12h.



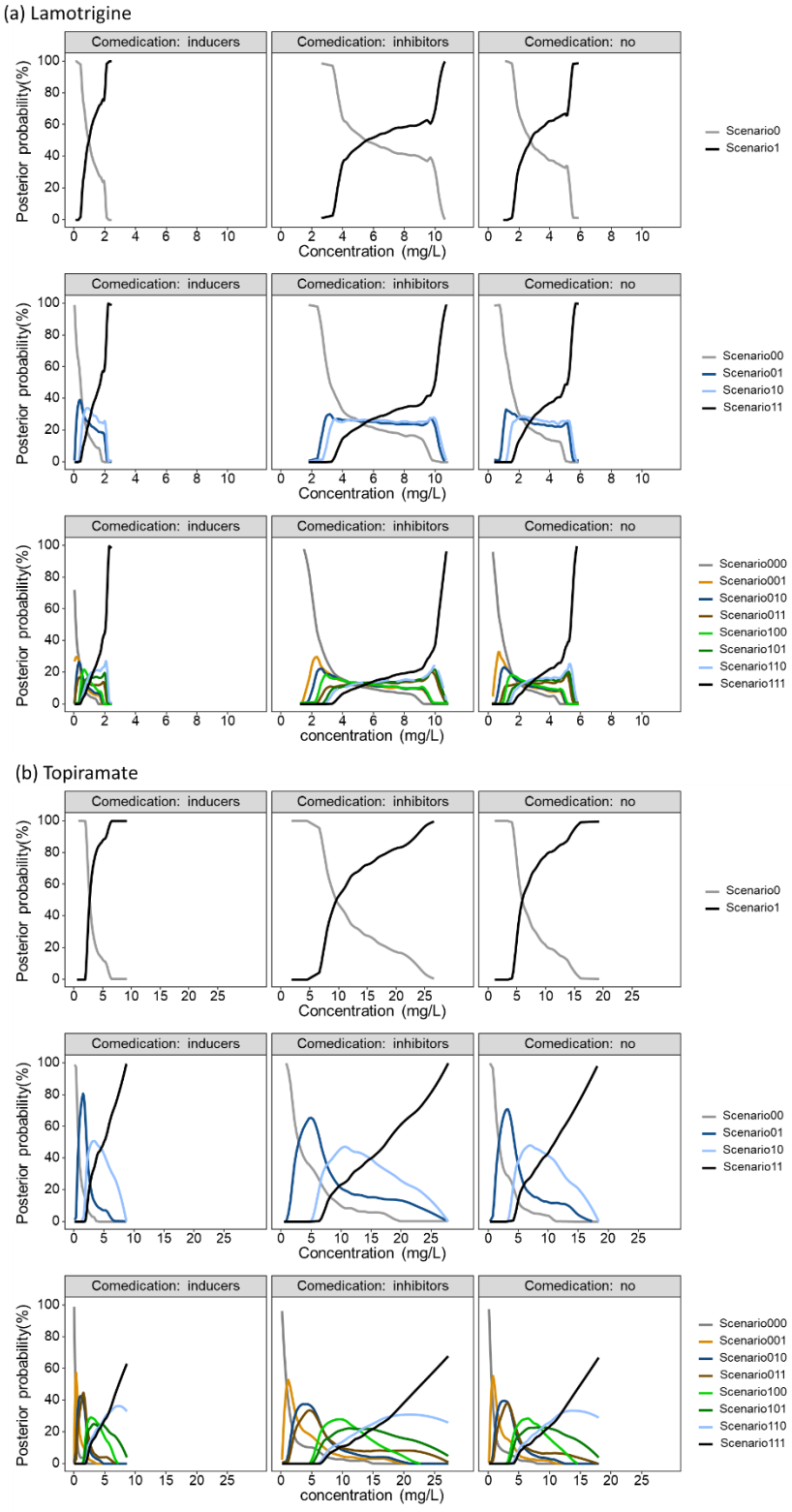
Appendix 19. Effect of renal function on the distinguishability of different dosing scenarios.

The virtual patients are adult, 40 years, 70 kg, taking levetiracetam tablet 500 mg q12h.



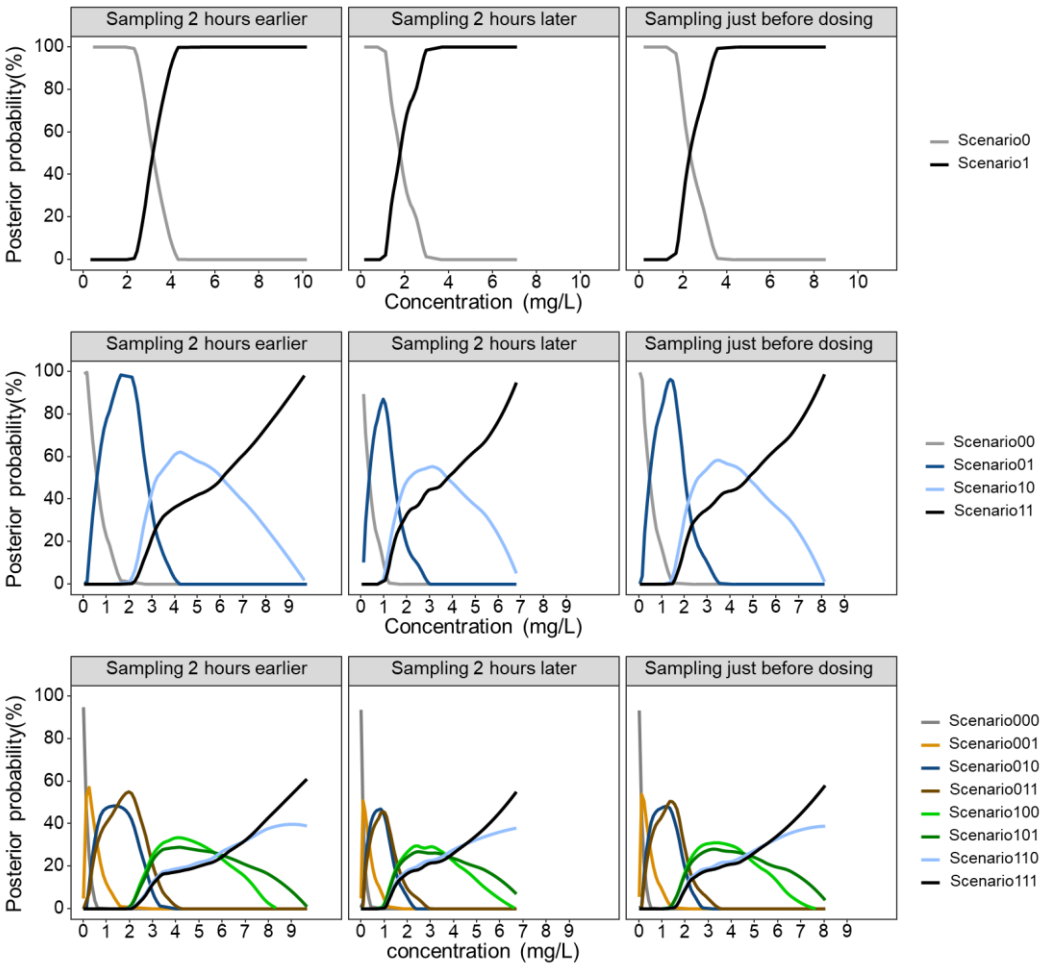
Appendix 20. Effect of concomitant medicine on the distinguishability of different dosing scenarios.

The virtual patients are adult, 40 years, 70 kg, CrCl 90 mL/min, taking lamotrigine tablet 100 mg q12h, or topiramate 200 mg q12h.



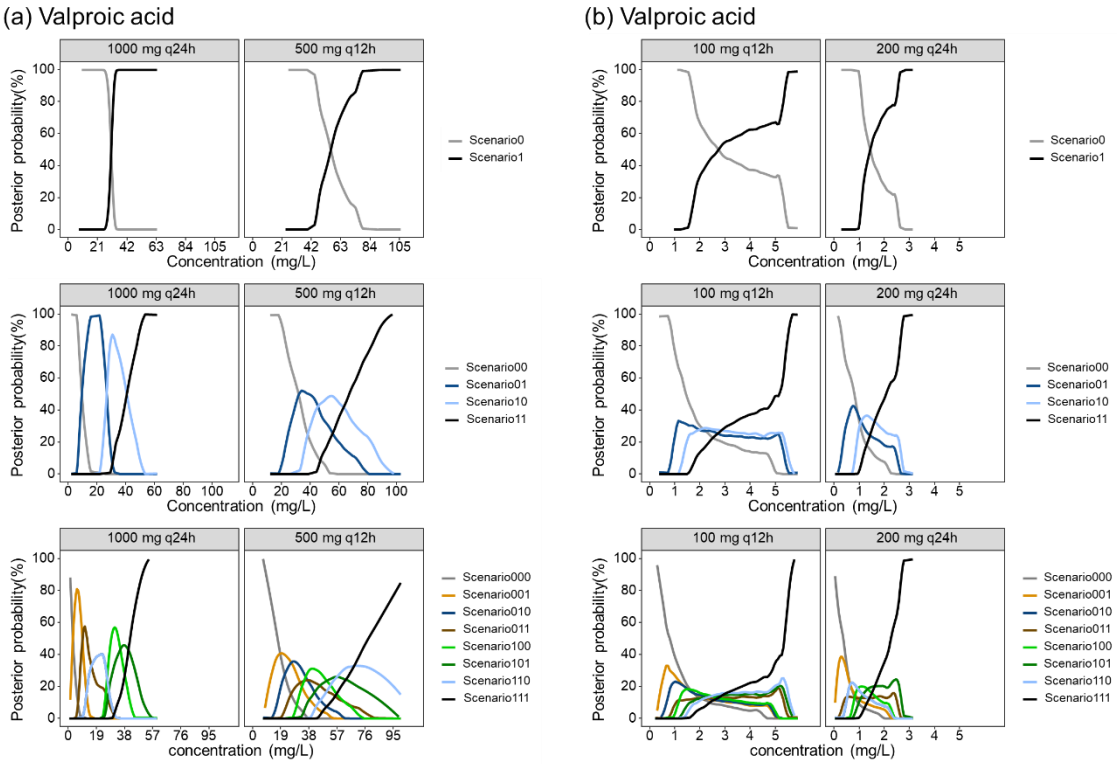
Appendix 21. Effect of sampling time on the distinguishability of dosing behaviors.

The virtual patients are adult, 40 years, 70 kg, 180 cm, taking levetiracetam tablet 500 mg q12h.



Appendix 22. Effect of dosing interval on the distinguishability of dosing behaviors.

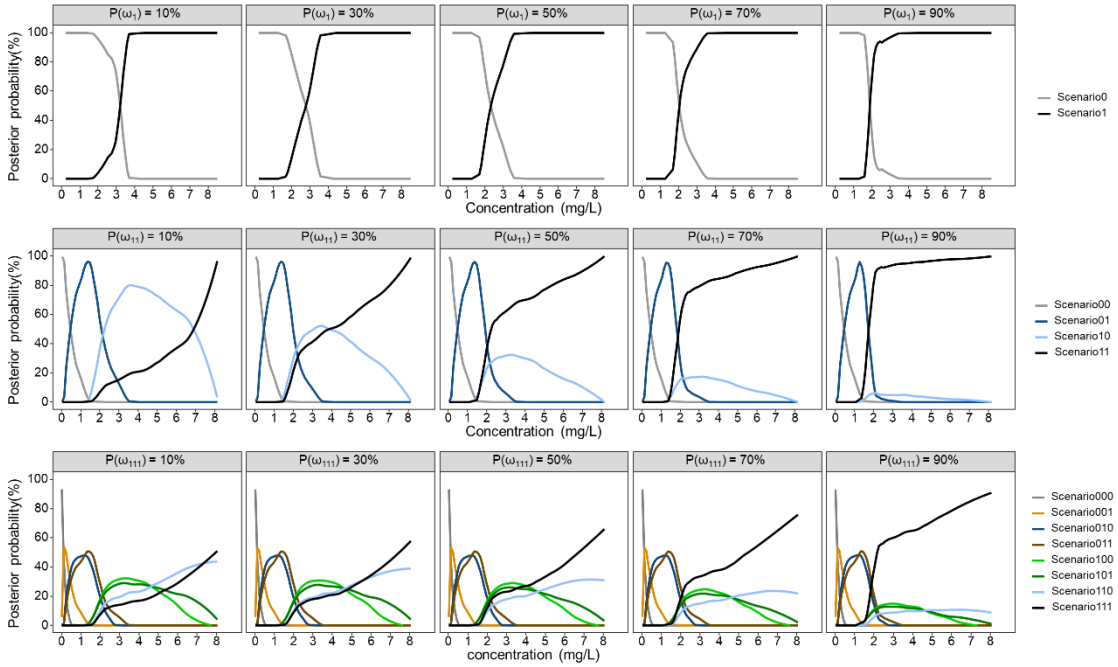
The virtual patients are adult, 40 years, 70 kg, 180 cm, taking valproic acid 500 mg q12h, or 1000 mg q24h; or taking lamotrigine 100 mg q12h, or 200 mg q24h.



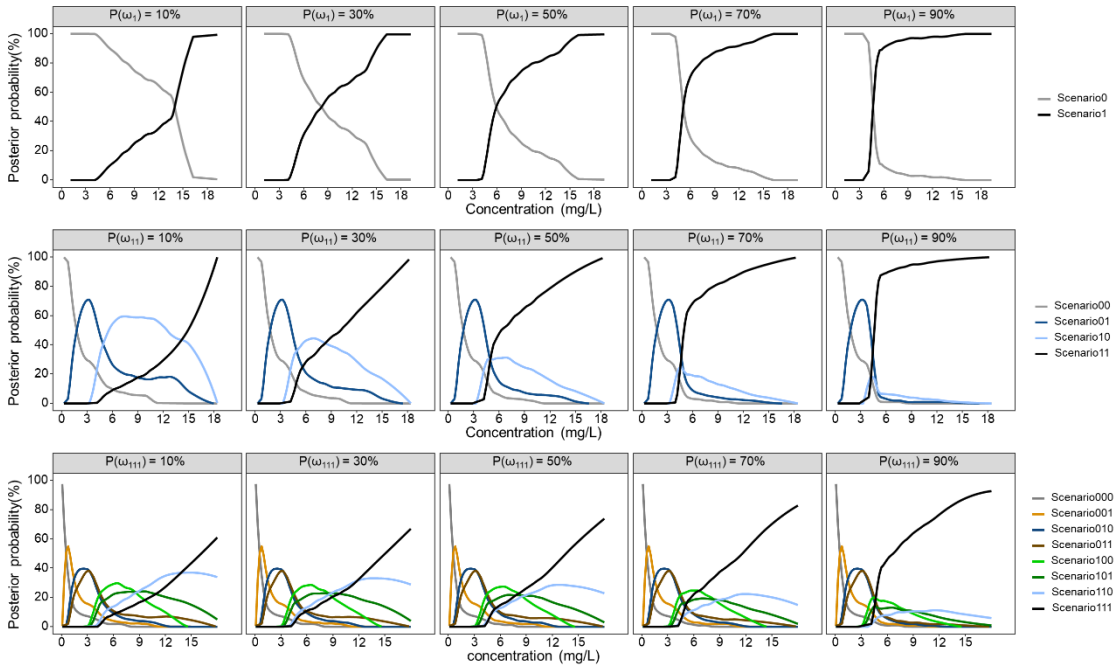
Appendix 23. Effect of prior probability on the distinguishability of dosing behaviors.

The virtual patients are adult, 40 years, 70 kg, 180 cm, taking levetiracetam 500 mg q12h, or topiramate 200 mg q12h.

(a) Levetiracetam



(b) Topiramate



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