

Supplementary material 4

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Physiologically Based Pharmacokinetic (PBPK) Modeling of Antidepressants: A Scoping Review of existing models, applications, and software-tools

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Supplementary File 4:
Overview table summarizing all extracted data
Table S1

General data									Assessment/Model development stage								
Title	First author	Year	Antidepressant(s)	Model purpose/ application	Perpetrator / victim	Software	Model type (antidepressant)	Metabolite modeled	Development / Refinement/ Parameter origin across all PBPK development stages (bottom up/ middle out/ top down) (0-6)	Robustness / Sensitivity Analysis across all PBPK development stages (local/ global/ none) (0-3)	Number of clinical studies in human used for validation (counting unique studies, not datasets)	Type of validation across all PBPK development stages (external/ external + internal/ internal only/ none) (0-5)	Scope of validation across all PBPK development stages (0-4)	Validation of the Final model / Final application (0-2)	Overall score (0-20)	Commentary	Model development stage
Utilizing Physiologically Based Pharmacokinetic Models to Support Rational Medication in Chinese Elderly Population	Wu et al.	2025	amitriptyline	geriatric (+ ethnicity)	n.a.	GastroPlus (version 9.8.2)	whole body	no	middle out (4) (the "verify & optimize" step is described generically; drug-specific optimisation details are not reported for amitriptyline individually)	no (0)	2 studies	internal (2)	< 5 studies, ≥2 doses, < 2 formulations (1)	no (0)	7	n.a.	intermediate
A four-compartment PBPK heart model accounting for cardiac metabolism - model development and application	Tytki et al.	2017	amitriptyline	cardiac	n.a.	R (version 3.3.0 and DeSolve package version 1.33); SimCyp for predicting Kp-values	whole body	no	middle out (4)	no (0)	1 study (+ 1 study with preclinical animal data as a reference for cardiac fitting)	internal (2)	< 5 studies, 1 dose, 1 formulation (0)	internal; 1 study (1)	7	n.a.	intermediate
The effect of increasing amitriptyline doses on cardiomyocytes' electrophysiology - Simulation study	Tytki et al.	2016	amitriptyline	cardiac	n.a.	SimCyp (version 14) (+ Cardiac Safety Simulator (CSS) version 2.0)	not clearly reported	yes	not classifiable; pre-existing model in new context	no (0)	n.a.	no validation of the new application context was performed	no validation of the new application context was performed	no validation of the new application context was performed	n.a.	base model: SimCyp compound file; Assessment refers only on the new application of this PBPK model; the compound file itself was not evaluated (no information available)	n.a.
A physiologically based pharmacokinetic (PBPK) model for predicting the efficacy of drug overdose treatment with liposomes in man	Howell et al.	2010	amitriptyline	toxicity/ drug overdose	n.a.	MATLAB	whole body	no	middle out (4)	no (0)	~7 studies	internal + external (4)	≥ 5 studies <10 studies; ≥ 2 doses; 2 formulations (3)	liposome overdose simulations: no validation (0)	11	n.a.	substantial
Mechanistic Physiologicly Based Pharmacokinetic (PBPK) Model of the Heart Accounting for Inter-Individual Variability: Development and Performance Verification	Tytki et al.	2018a	amitriptyline, nortriptyline (metabolite)	cardiac	n.a.	R (version 3.4.0 and deSolve package version 1.14)	whole body	yes	middle out (4)	no (0)	4 studies	internal + external (4)	< 5 studies, ≥ 2 doses, 1 formulation (1)	internal + external; 4 studies (2)	11	n.a.	substantial
Physiologically based pharmacokinetic modelling predicts altered maternal pharmacokinetics of amitriptyline during pregnancy	Scherf-Clavel et al.	2025	amitriptyline, nortriptyline (metabolite)	pregnancy	n.a.	PK-Sim (version 11)	whole body	yes	middle out (4)	local (1)	12 studies (own data counted as one study only)	mainly external (5)	≥ 10 studies; ≥ 2 doses, ≥2 formulations (4)	external; 1 study (1)	15	n.a.	extensive
Physiologically based pharmacokinetic-quantitative systems toxicology and safety (PBPK-QS) modeling approach applied to predict the variability of amitriptyline pharmacokinetics and cardiac safety in populations and in individuals	Tytki et al.	2018b	amitriptyline, nortriptyline (metabolite)	cardiac	n.a.	R (version 3.4.1)	whole body	yes	middle out (4) (base model: Tytki et al. (2018a); middle out, extended model: middle out)	no (0)	33 studies (base model: Tytki et al. (2018a); 4 studies; extended model: 29 studies); 4 internal; 29 external	internal + external (4)	≥ 10 studies; ≥ 2 doses, 2 formulations (4)	internal + external; 29 studies (2) (the oral (PO) PBPK model was considered the final model)	14	n.a.	extensive
Physiologically Based Pharmacokinetic Model of CYP2D6 Associated Interaction Between Venlafaxine and Strong Inhibitor Bupropion-The Influence of Age- Relevant Changes and Inhibitory Dose to Classify Therapeutic Success and Harm	Luecht et al.	2025	bupropion	DDI (+ geriatric)	inhibitor (CYP2D6)	PK-Sim and MoBi (version 9.1)	whole body	yes	middle out (4)	no (0)	6 studies + data from KOBAS database (counted as 1 additional study)	internal (2)	≥ 5 studies <10 studies, ≥ 2 doses, 1 formulation (2)	no (0) (BUP only indirectly assessed via VEN/DOV trough concentrations in DDI scenarios)	8	n.a.	intermediate
Physiologically based pharmacokinetic model to predict drug concentrations of breast cancer resistance protein substrates in milk	Zhang et al.	2022	bupropion	lactation	n.a.	SimCyp (version 21.1)	whole body	no	base model: SimCyp default compound file; extended model: middle out (4)	no (0)	1 study	internal (2)	< 5 studies, 1 dose, 1 formulation (0)	internal; 1 study (1)	7	base model: SimCyp compound file; assessment refers only to the model built upon the Simcyp compound file; the compound file itself was not evaluated (no information available)	intermediate
A Bayesian population physiologically based pharmacokinetic absorption modeling approach to support generic drug development: application to bupropion hydrochloride oral dosage forms.	Hsieh et al.	2021	bupropion	drug formulation	n.a.	R (RStudio; pksemi package); GNU MCSim (version 6.1.0)	semiphysiological PBPK	no	middle out (4)	global (3)	1 study (cross-validation / hold-out design within one study)	internal (2)	< 5 studies, ≥ 2 doses, ≥ 2 formulations (2)	virtual BE application model; no validation (0)	11	n.a.	substantial
Differences in cytochrome p450-mediated pharmacokinetics between chinese and caucasian populations predicted by mechanistic physiologically based pharmacokinetic modelling	Barter et al.	2013	bupropion	ethnicity	n.a.	SimCyp (version 11.1)	minimal PBPK	yes	predominantly bottom up (6)	no (0)	1 study	internal (2); same study for bupropion (external); and metabolite (internal); overall validation classified as internal, as the sole validation study also informed metabolite model parameterisation.	< 5 studies; 1 dose; 1 formulation (0)	final parent-metabolite PBPK model: internal; 1 study (1)	9	base model: SimCyp compound file; assessment refers only to the model built upon the Simcyp compound file (extended model); the compound file itself was not evaluated (no information available)	substantial
A Comprehensive CYP2D6 Drug-Gene Interaction Network for Application in Precision Dosing and Drug Development	Rüdesheim et al.	2025	bupropion	DDI/GI	inhibitor (CYP2D6)	PK-Sim and MoBi (version 11)	whole body	yes	base model (Marok); middle out; extended model: bottom up (4)	base model (Marok); local (1)	base model (Marok); ~38 studies; no validation of extended model/ application	internal + external (4)	≥ 10 studies, ≥ 2 doses, ≥2 formulations (4)	no (0)	13	n.a.	extensive

Physiologically Based Pharmacokinetic Modeling of Bupropion and Its Metabolites in a CYP2B6 Drug-Gene Interaction Network	Marok et al.	2021	bupropion	D/D/GI	victim (CYP2B6)	PK-Sim and MoBi (version 9.1)	whole body	yes	middle out (4)	local (1)	~ 38 studies	internal + external (4)	≥ 10 studies, ≥ 2 doses, ≥2 formulations (4)	internal; 2 studies (2)	15	n.a.	extensive
Prediction of Drug-Drug Interactions with Bupropion and Its Metabolites as CYP2D6 Inhibitors Using a Physiologically-Based Pharmacokinetic Model	Xue et al.	2017	bupropion	DDI	inhibitor (CYP2D6)	SimCyp (version 15)	whole body	yes	middle out (4)	local (1)	5 studies	internal + external (4)	≥ 5 studies <10 studies, ≥ 2 doses, 1 formulation (2)	internal; 1 study (1)	12	n.a.	substantial
Utilizing Physiologically Based Pharmacokinetic Models to Support Rational Medication in Chinese Elderly Population	Wu et al.	2025	citalopram	geriatric (+ ethnicity)	n.a.	GastroPlus (version 9.8.2)	whole body	no	middle out (4) (the "verify & optimize" step is described generically; drug-specific optimisation details are not reported for citalopram individually)	no (0)	2 studies	internal (2)	< 5 studies, ≥2 doses, < 2 formulations (1)		7	n.a.	intermediate
Physiologically Based Pharmacokinetic Approach Can Successfully Predict Pharmacokinetics of Citalopram in Different Patient Populations	Wu et al.	2020	citalopram	geriatric (+ pharmacogenetics)	n.a.	SimCyp (version 15.1)	whole body	no	middle out (4)	local (1)	11 studies	internal + external (4)	≥ 10 studies, ≥ 2 doses, ≥2 formulations (4)	external; 7 studies (2)	15	n.a.	extensive
Prediction of drug-drug interactions between various antidepressants and efavirenz or boosted protease inhibitors using a physiologically based pharmacokinetic modeling approach.	Siccardi et al.	2013	citalopram	DDI	victim (CYP3A4, CYP2C19, CYP2D6)	SimCyp (version 10.1)	full or simple PBPK model (note: simple PBPK likely represents a reduced PBPK structure analogous to a minimal PBPK framework; however, the exact structural implementation is not described sufficiently to allow definitive classification)	no	bottom up (6)	no (0)	n.a.	informal comparison (0) (note: 0 points because no formal validation framework or independent, predefined validation datasets are described, and all comparisons are limited to informal post hoc agreement of simulated and observed data)	n.a.	n.a.	6	base model: SimCyp compound file; assessment refers only to the model built upon the Simcyp compound file (extended model); the compound file itself was not evaluated (no information available)	intermediate
Inhibitory Effects of Tricyclic Antidepressants on Human Liver Microsomal Morphine Glucuronidation: Application of NWE to Predict Potential Drug-Drug Interactions in Humans	Uchaipichat	2023	clomipramine	DDI	inhibitor (UGT, OCT1)	SimCyp (version 20.1)	minimal PBPK	no	mainly bottom-up (6)	local (1)	3 studies	internal (2)	< 5 studies, ≥ 2 doses, 1 formulation (1)		10	n.a.	substantial
Development of Biopredictive Dissolution Method for Extended-Release Desvenlafaxine Tablets	Carapeto et al.	2023	desvenlafaxine	drug formulation	n.a.	GastroPlus (version 9.8.3) (for lysosomal trapping: MembranePlus)	semiphysiological PBPK	no	bottom-up, middle-out and top-down approaches (overall middle-out) (4)	local (1)	1 study (base model and refined model (R Tablet); 1 study (internal); final application model (VBE for ER Tablets); only in silico; Generic #3 as external formulation test (not counted as a study))	mostly internal (2)	< 5 studies, ≥ 2 doses, ≥2 formulations (2)	final application model (VBE for ER Tablets); no (0) (external formulation test does not qualify as clinical study)	9	n.a.	substantial
In vitro solubility, dissolution and permeability studies combined with semi-mechanistic modeling to investigate the intestinal absorption of desvenlafaxine from an immediate- and extended-release formulation	Frank et al.	2015	desvenlafaxine	drug formulation	n.a.	SimCyp (version 13.2)	semiphysiological PBPK	no	middle-out (4)	local (1)	9 studies	internal + external (4)	≥ 5 studies <10 studies; ≥ 2 doses; ≥ 2 formulations (3)	internal + external; 7 studies (2) (M5 was considered the fina model because it represents the most mechanistically comprehensive and fully refined version)	14	the models M1-M5 were treated as iterative refinement stages of one PBPK model, not separate models, since they shared the same structural disposition framework and differed only in absorption model implementation; M5 is considered the final application model	extensive
Utilizing Physiologically Based Pharmacokinetic Models to Support Rational Medication in Chinese Elderly Population	Wu et al.	2025	doxepin	geriatric (+ ethnicity)	n.a.	GastroPlus (version 9.8.2)	whole body	no	middle out (4) (the "verify & optimize" step is described generically; drug-specific optimisation details are not reported for doxepin individually)	no (0)	1 study (3 mg only); cave: validation was performed at a dose far below the antidepressant dose range; no validation at therapeutic antidepressant doses	internal (2)	< 5 studies, <2 doses, < 2 formulations (0)		6	n.a.	intermediate
Exploratory Translational Modeling Approach in Drug Development to Predict Human Brain Pharmacokinetics and Pharmacologically Relevant Clinical Doses	Kriebase et al.	2012	duloxetine	brain exposure/ CNS targeting	n.a.	NONMEM (version V, level 1.1)	semiphysiological PBPK	no	middle out (4)	no (0)	no studies	no validation (0)	n.a.	n.a.	4	not PBPK model was validated only using initial animal data and is not counted as a validation study in this human-focused assessment. The final human model is supported only by indirect qualitative comparisons to clinical PD/biomarker data, which do not constitute formal quantitative validation	initial
Pharmacokinetics of duloxetine self-administered in overdose with quetiapine and other antipsychotic drugs in a Japanese patient admitted to hospital	Adachi et al.	2021	duloxetine	toxicity/ drug overdose	n.a.	n.a.	minimal PBPK	no	middle out (4)	no (0)	1 study (case report with single adult overdose patient used for illustrative comparison only)	internal (2)	< 5 studies; 1 dose; 1 formulation (0)	internal validation; 1 study (1)	7	n.a.	intermediate
Physiologically-Based Pharmacokinetic Modeling for the Prediction of CYP2D6-Mediated Gene-Drug Interactions	Storelli et al.	2019	duloxetine	D/D/GI	inhibitor (CYP2D6)	SimCyp (version 17)	whole body	no	middle out (4)	local (1)	11 studies (PK validation: 7, DOI validation: 3, DDGI validation: 1)	internal + external (4)	≥ 10 studies, ≥ 2 doses, ≥2 formulations (4)	internal; 1 study (1)	14	n.a.	extensive
Impact of CYP2C19 Phenotype on Escitalopram Response in Geriatrics: Based on Physiologically-Based Pharmacokinetic Modeling and Clinical Observation	Jang et al.	2025	escitalopram	geriatric (+ pharmacogenetics)	n.a.	SimCyp (version 22)	whole body	no	middle out (4)	no (0)	5 studies	external (3)	≥ 5 studies <10 studies, ≥ 2 doses, 1 formulation (2)	external; 1 study (1)	12	n.a.	substantial
Application of Lactation Physiologically Based Pharmacokinetic Modeling to Predict Milk Exposure of Passively Diffused Drugs	Kayesh et al.	2025	escitalopram	lactation	n.a.	SimCyp (version n.a.)	minimal PBPK	no	middle out (4)	local (1)	4 studies	external (5)	< 5 studies, ≥ 2 doses, 1 formulation (1)	external; 1 study (1)	12	n.a.	substantial

Escitalopram Dose Optimization During Pregnancy: A PBPK Modeling Approach	Choi et al.	2025	escitalopram	pregnancy (+ pharmacogenetics)	n.a.	SimCyp (version n.a.)	whole body	no	middle out (4)	global (3)	6 studies	internal + external (4)	≥ 5 studies <10 studies, ≥ 2 doses, 1 formulation (3)	external; 1 study (1)	14	n.a.	extensive
Safety of medicines during breastfeeding - from case report to modeling: a contribution from the ConcoTIGON project	Cardoso et al.	2023	escitalopram	lactation	n.a.	PK-Sim (version: n.a.)	whole body	no	middle out (4) (base model from Delaney et al. (2018); middle out; extended model: bottom up)	no (0)	7 studies (base model: Delaney (2018); 6 studies; extended model: 1 study)	internal + external (4)	≥ 5 studies <10 studies, ≥ 2 doses, 2 formulations (3)	breastfed infant PBPK model: 1 study (1); external validation with very limited data	12	no access to supplementary material provided	substantial
Predicting Escitalopram Exposure to Breastfeeding Infants: Integrating Analytical and In Silico Techniques	Delaney et al.	2018	escitalopram	lactation	n.a.	PK-Sim (version 6.3); Simulation of infant daily doses: performed using MATLAB	whole body	no	middle out (4)	no (0)	6 studies	internal + external (4)	≥ 5 studies <10 studies, ≥ 2 doses, 2 formulations (3)	external; 1 study (1)	12	n.a.	substantial
Prediction of Maternal and Fetal Exposure to Escitalopram, Sertraline, and Paroxetine by Combining Human Ex Vivo Placenta Perfusion Data and Physiologically Based Pharmacokinetic Modeling	Préta et al.	2025	escitalopram	pregnancy	n.a.	SimCyp (version 22)	whole body	no	middle out (4)	no (0)	11 studies	internal + external (4) (Nonpregnant Healthy Volunteer Base PBPK Model: separation between refinement studies and validation studies not clearly documented)	≥ 10 studies, ≥ 2 doses, 1 formulation (2)	external; 3 studies (2)	13	n.a.	extensive
Prediction of Drug-Drug Interactions After Esketamine Intranasal Administration Using a Physiologically Based Pharmacokinetic Model	Willemin et al.	2022	esketamine	DDI	inductor, inhibitor, victim (CYP3A4)	SimCyp (version 14.1)	whole body	yes	middle out (4)	no (0)	10 studies	internal + external (4)	≥ 10 studies, ≥ 2 doses, ≥ 2 formulations (4)	external; 1 study (1)	13	n.a.	extensive
Estimation of Bioavailable Concentration of Endogenously Formed N-Nitrosamines by Physiologically Based Kinetic Modeling	Spaenig et al.	2025	fluoxetine	toxicity/ drug overdose	n.a.	R (RStudio 2023.12.0; deSolve package)	whole body	no	mostly bottom up (6)	local (1)	2 studies	external (5)	2 studies, 2 doses, 1 formulation (1)	external; 2 studies (2)	15	Only the fluoxetine PBPK model was assessed. The separately presented N-nitrosofluoxetine model was excluded, as it represents a nitrosamine impurity rather than a pharmacologically active metabolite directly linked to the fluoxetine PBK model	extensive
Utilizing Physiologically Based Pharmacokinetic Models to Support Rational Medication in Chinese Elderly Population	Wu et al.	2025	fluoxetine	geriatric (+ ethnicity)	n.a.	GastroPlus (version 9.8.2)	whole body	no	middle out (4) (the "verify & optimize" step is described generically; drug-specific optimization details are not reported for fluoxetine individually)	no (0)	2 studies	internal (2)	< 5 studies, <2 doses, <2 formulations (0)		6	n.a.	intermediate
Prediction of basic drug exposure in milk using a lactation model algorithm integrated within a physiologically based pharmacokinetic model	Pansari et al.	2022	fluoxetine	lactation	n.a.	SimCyp (version 20)	minimal PBPK	no	base model: SimCyp default compound file; extended model: bottom up (6)	local (1)	2 studies (with a third referenced supportively)	external (5)	< 5 studies, ≥ 2 doses, 1 formulation (1)	external; 2 studies (2)	15	base model: SimCyp compound file; assessment refers only to the model built upon the Simcyp compound file; the compound file itself was not evaluated (no information available)	extensive
Prediction of Fluoxetine and Norfluoxetine Pharmacokinetic Profiles Using Physiologically Based Pharmacokinetic Modeling	Jeong et al.	2021	fluoxetine	ethnicity	n.a.	SimCyp (version 19)	whole body	yes	middle out (4)	no (0)	2 studies	internal (2)	< 5 studies, ≥ 2 doses, 1 formulation (1)	no validation (0)	7	base model: SimCyp compound file; assessment refers only to the model built upon the Simcyp compound file; the compound file itself was not evaluated (no information available)	intermediate
Physiologically Based Pharmacokinetic Modeling for the Prediction of CYP2D6-Mediated Gene-Drug Interactions	Storelli et al.	2019	fluoxetine	D/D/GI	inhibitor (CYP2D6)	SimCyp (version 17)	minimal PBPK	no	middle out (4)	no (0)	2 studies (only DDGI validation)	internal + external (4)	< 5 studies; 1 dose; 1 formulation (0)	internal + external; 2 studies (2)	10	base model: SimCyp compound file; assessment refers only to the model built upon the Simcyp compound file; the compound file itself was not evaluated (no information available)	substantial
Fluoxetine- and norfluoxetine-mediated complex drug-drug interactions: In vitro to In vivo correlation of effects on CYP2D6, CYP2C19, and CYP3A4	Sager et al.	2014	fluoxetine	DDI	inhibitor (CYP2D6, CYP3A4, and CYP2C19)	SimCyp (version 12)	semiphysiological PBPK	yes	middle out (4)	no (0)	3 studies	internal + external (4)	< 5 studies; < 2 doses; 1 formulation (0)	DDI prediction model: internal; 1 study (1)	9	Studies used for internal validation of the norfluoxetine model were not clearly described or identifiable, preventing unambiguous classification of the internally reused datasets	substantial
Prediction of drug-drug interactions between various antidepressants and efavirenz or boosted protease inhibitors using a physiologically based pharmacokinetic modelling approach	Siccardi et al.	2013	fluoxetine	DDI	victim (CYP2C9, CYP2C19 and CYP2D6)	SimCyp (version 10.1)	full or simple PBPK model (note: simple PBPK likely represents a reduced PBPK structure analogous to a minimal PBPK framework; however, the exact structural implementation is not described sufficiently to allow definitive classification)	no	bottom up (6)	no (0)	n.a.	informal comparison based on DDl ratios from regulatory sources (0) (note: 0 points because no formal validation framework or independent, predefined validation datasets are described, and all comparisons are limited to informal post hoc agreement of simulated and observed data)	n.a.	n.a.	6	base model: SimCyp compound file; assessment refers only to the model built upon the Simcyp compound file (extended model); the compound file itself was not evaluated (no information available)	intermediate
A Physiologically-Based Pharmacokinetic (PBPK) Model Network for the Prediction of CYP1A2 and CYP2C19 Drug-Drug Gene Interactions with Fluvoxamine, Omprazole, S-mephenytoin, Moclobemide, Tizanidine, Mexiletine, Ethinylestradiol, and Caffeine	Kanacher et al.	2020	fluvoxamin	D/D/GI	inhibitor (CYP1A2, CYP2C19)	PK-Sim (version 7.2.2 or higher); a re-qualification work in version 9.1	whole body	no	middle out (4)	local (1)	14 studies	internal + external (4)	≥ 10 studies, ≥ 2 doses, ≥ 2 formulations (4)	final application model: DDl; 2 formulations (4)	15	n.a.	extensive
A Comprehensive CYP2D6 Drug-Drug Gene Interaction Network for Application in Precision Dosing and Drug Development	Rüdesheim et al.	2025	fluvoxamine	D/D/GI	inhibitor (CYP2D6, CYP3A4)	PK-Sim and MoBi (version 11)	whole body	no	middle out (base model (Britz); middle out; extended model: bottom up) (4)	base model (Britz); local (1)	base model (Britz): 31 studies; no validation of final (extended) model	internal + external (4)	≥ 10 studies, ≥ 2 doses, ≥ 2 formulations (4)	no (0)	13	n.a.	extensive

aber: Suppression v.a. als Modellsubstrat für CYP2D6 Substrate; (AS ausgewählt, die überwiegend über spezifische CYP-Enzyme metabolisiert + nur minimaler Einfluss von Transportern) (Suppression bzw. hydroxypropion für CYP2D6-Aktivität) --> Fazit: klin. relevante Aussage überwiegt, daher include!

Physiologically-Based Pharmacokinetic Models for CYP1A2 Drug-Drug Interaction Prediction: A Modeling Network of Fluvoxamine, Theophylline, Caffeine, Risperidone, and Midazolam	Britz et al.	2019	fluvoxamine	DDI	inhibitor (CYP3A4)	PK-Sim and MoBi (version 7.3.0)	whole body	no	middle out (4)	local (1)	31 studies (base model and refined fluvoxamine model: 26 studies (internal: 9, external: 17 studies); final model: DDI Application Model (fluvoxamine as perpetrator): 5 studies (external))	internal + external (4)	> 10 studies; > 2 doses, >2 formulations (4)	external: 5 studies (2)	15	n.a.	extensive
Utilizing Physiologically Based Pharmacokinetic Models to Support Rational Medication in Chinese Elderly Population	Wu et al.	2025	fluvoxamine	geriatric (+ ethnicity)	n.a.	GastroPlus (version 9.8.2)	whole body	no	middle out (4) (the "verify & optimize" step is described generically; drug-specific optimisation details are not reported for fluvoxamine individually)	no (0)	2 studies	internal (2)	< 5 studies; >2 doses, 1 formulation (1)	no (0)	7	n.a.	intermediate
Prediction of CYP-Mediated Drug Interaction Using Physiologically Based Pharmacokinetic Modeling: A Case Study of Subutamol and Fluvoxamine	Marques et al.	2023	fluvoxamine	DDI	inhibitor (CYP2C19, CYP2D6)	GastroPlus (version 9.8.3)	not clearly reported (GastroPlus-verified PBPK model)	no	not classifiable (base model: GastroPlus-verified PBPK model; applied in DDI context by providing CYP inhibition parameters)	no (0)	base model validation: n.a.; no validation of fluvoxamine model in DDI context	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
Optimising Fluvoxamine Maternal/Fetal Exposure during Gestation: A Pharmacokinetic Virtual Clinical Trials Study	Burhanuddin et al.	2022	fluvoxamine	pregnancy (+ pharmacogenetics)	n.a.	SimCyp (version 20)	whole body	no	middle out (4)	local (1)	14 studies	internal + external (4)	> 10 studies; > 2 doses, 1 formulation (3)	fetoplacental PBPK model: external: 3 studies; Final Application Model (CYP2D6 Phenotype Dose Optimisation): no validation (0)	12	n.a.	substantial
Quantitative prediction of fetal plasma concentration of fluvoxamine during dosage tapering to the mother	Matsuoka et al.	2017	fluvoxamine	pregnancy	n.a.	HLAB	semiphysiological PBPK	no	middle out (4)	no (0)	1 study (+ 1 additional study: only contained in vitro data and was therefore not considered in this assessment)	as the external validation study contained only a single data point, it was not considered a full validation study in this assessment. Therefore, validation was rated as absent in this case. Nevertheless, inclusion of the data point in the final model assessment ensured that the external study was still acknowledged. (0)	< 5 studies; < 2 doses, 1 formulation (0)	external: 1 study (1) (cave: only 1 data point (single case, single time point))	5	n.a.	intermediate
Development of a Physiologically Based Pharmacokinetic/Pharmacodynamic Model to Predict the Impact of Genetic Polymorphisms on the Pharmacokinetics and Pharmacodynamics Represented by Receptor/Transporter Occupancy of Central Nervous System Drugs	Alqahtani et al.	2016	fluvoxamine	brain exposure/ CNS targeting (+ pharmacogenetics)	n.a.	GastroPlus (version 8.5)	whole body	no	middle out (4)	no (0)	4 studies	internal + external (4)	< 5 studies; > 2 doses; 1 formulation (1)	internal + external: 2 studies (2) (the CYP2D6-PK-PBPK model was considered the final model)	11	n.a.	substantial
Pharmacokinetic modeling of non-linear brain distribution of fluvoxamine in the rat	Geldof et al.	2007	fluvoxamine	brain exposure/ CNS targeting	n.a.	n.a.	semiphysiological PBPK	no	middle out (4)	no (0)	1 study	internal (2)	< 5 studies; < 2 doses; 1 formulation (1)	internal: 1 study (1)	8	note1: paper describes a preclinical rat PBPK/brain distribution model rather than a human PBPK model, therefore animal studies were considered appropriate and were included in the validation assessment; note2: A previously published empirical three-compartment population PK model for fluvoxamine (Geldof et al., 2007) was used to generate the systemic plasma concentration input for the semi-physiological brain distribution model; assessment only refers to the PBPK model	intermediate
Use of three-compartment physiologically based pharmacokinetic modeling to predict hepatic blood levels of fluvoxamine relevant for drug-drug interactions	Iga	2014	fluvoxamine	DDI	inhibitor (CYP1A2, CYP2C19)	n.a.	minimal PBPK	no	middle out (4)	local (1)	1 study	internal (2)	< 5 studies; < 2 doses; 2 formulations (1)	internal: 1 study (1)	9	n.a.	substantial
Physiologically Based Pharmacokinetic Model of Brain Delivery of Plasma Protein Bound Drugs	Partridge	2023	imipramine	brain exposure/ CNS targeting	n.a.	Mathematica (version 12.3.1.0) (note: Mathematica was used as a general mathematical modelling environment to implement and numerically solve the PBPK model equations and simulate concentration-time profiles)	semiphysiological PBPK	no	mainly bottom-up (6)	local (1)	3 studies with preclinical (animal) data	no validation (only qualitative comparison with preclinical animal data) (0)	n.a.	n.a.	7	n.a.	intermediate
Inhibitory Effects of Tricyclic Antidepressants on Human Liver Microsomal Morphine Glucuronidation: Application of NWE to Predict Potential Drug-Drug Interactions in Humans	Uchaipichat	2023	imipramine	DDI	inhibitor (UGT, OCT1)	SimCyp (version 20.1)	not clearly reported ("verified oral SimCyp no default mode")	no	base model, SimCyp compound file; not classifiable; DDI model: only 2 additional parameters incorporated into the model (experimental- and literature-derived); overall: not classifiable (n.a.)	local (1)	validated SimCyp compound file; no validation information in present paper; not classifiable; DDI model: no (n.a.)	not classifiable	not classifiable	no (0)	n.a.	n.a.	n.a.

Use of three-compartment physiologically based pharmacokinetic modeling to predict hepatic blood levels of fluvoxamine relevant for drug-drug interactions	Iga	2014	imipramine	DDI	victim (CYP1A2, CYP2C19)	n.a.	minimal PBPK	no	middle out (4)	no (0)	1 study	internal (2)	< 5 studies; 2 doses; 2 formulations (2)	internal; 1 study (1)	9	n.a.	substantial
Prediction of drug-drug interactions between various antidepressants and efavirenz or boosted protease inhibitors using a physiologically based pharmacokinetic modeling approach	Siccardi et al.	2013	mirzapine	DDI	victim (CYP3A4, CYP2D6, CYP2C8)	SimCyp (version 10.1)	full or simple PBPK model (note: simple PBPK likely represents a reduced PBPK structure analogous to a minimal PBPK framework; however, the exact structural implementation is not described sufficiently to allow definitive classification)	no	bottom up (6)	no (0)	n.a.	no validation of the extended model and the new application context was performed (0)	n.a.	n.a.	6	base model: SimCyp compound file; assessment refers only to the model built upon the Simcyp compound file (extended model); the compound file itself was not evaluated (no information available)	intermediate
Utilizing Physiologically Based Pharmacokinetic Models to Support Rational Medication in Chinese Elderly Population	Wu et al.	2025	moclobemide	geriatric (+ ethnicity)	n.a.	GastroPlus (version 9.8.2)	whole body	no	middle out (4) (the "verify & optimize" step is described generically; drug-specific optimisation details are not reported for moclobemide individually)	no (0)	2 studies	internal (2)	< 5 studies; >2 doses, 1 formulation (1)	no (0)	7	n.a.	intermediate
A Physiologically Based Pharmacokinetic (PBPK) Model Network for the Prediction of CYP1A2 and CYP2C19 Drug-Drug Gene Interactions with Fluvoxamine, Omeprazole, S-mephenytoin, Moclobemide, Tizanidine, Mexiletine, Ethinylestradiol, and Caffeine	Kanacher et al.	2020	moclobemide	D/Di/GI	inhibitor + victim (CYP2C19)	PK-Sim (version 7.2.2 or higher); (a re-qualification work in version 9.1)	whole body	no	middle out (4)	local (1)	6 studies	internal + external (4)	> 5 studies <10 studies, > 2 doses, > 2 formulations (3)	final application model: DDI model with moclobemide as perpetrator/ victim; internal + external; 2 studies (2)	14	n.a.	extensive
Risk assessment of accidental nortriptyline poisoning: the importance of cytochrome P450 for nortriptyline elimination investigated using a population-based pharmacokinetic simulator	Jornil et al.	2011	nortriptyline	toxicity/ drug overdose (+ pharmacogenetics)	n.a.	SimCyp (version 10.00)	minimal PBPK	no	middle out (4)	no (0)	11 studies	internal + external (4)	> 10 studies; > 2 doses; 1 formulation (2)	1 risk assessment applications; no validation (0)	11	n.a.	substantial
Utilizing Physiologically Based Pharmacokinetic Models to Support Rational Medication in Chinese Elderly Population	Wu et al.	2025	nortriptyline	geriatric (+ ethnicity)	n.a.	GastroPlus (version 9.8.2)	whole body	no	middle out (4) (the "verify & optimize" step is described generically; drug-specific optimisation details are not reported for nortriptyline individually)	no (0)	1 study	internal (2)	< 5 studies, <2 doses, 1 formulation (0)	no (0)	6	n.a.	intermediate
Utilizing Physiologically Based Pharmacokinetic Models to Support Rational Medication in Chinese Elderly Population	Wu et al.	2025	paroxetine	geriatric (+ ethnicity)	n.a.	GastroPlus (version 9.8.2)	whole body	no	middle out (4) (the "verify & optimize" step is described generically; drug-specific optimisation details are not reported for paroxetine individually)	no (0)	1 study	internal (2)	< 5 studies, <2 doses, 1 formulation (0)	no (0)	6	n.a.	intermediate
Prediction of Maternal and Fetal Exposure to Escitalopram, Sertraline, and Paroxetine by Combining Human Ex Vivo Placenta Perfusion Data and Physiologically Based Pharmacokinetic Modeling	Pfritta et al.	2025	paroxetine	pregnancy	n.a.	SimCyp (version 22)	whole body	no	bottom up (6) (model development based on the Simcyp compound file was assumed to represent a bottom-up approach; Simcyp compound file previously validated by Abduljalil (2020) and Jornil (2010))	no (0)	6 studies	external (5)	> 5 studies <10 studies, 1 dose, 1 formulation (1)	external; 3 studies (2)	14	n.a.	extensive
Prediction of basic-drug exposure in milk using a lactation model algorithm integrated within a physiologically based pharmacokinetic model	Pansari et al.	2022	paroxetine	lactation	n.a.	SimCyp (version 20)	minimal PBPK	no	base model: SimCyp default compound file; extended model: bottom up (6)	no (0)	base model: 2 studies (not clearly described whether these studies represent internal or external validation studies); extended model: 1 study (external)	external (5)	< 5 studies, > 2 doses, 1 formulation (1)	external; 1 study (1)	13	n.a.	extensive
Physiologically Based Pharmacokinetic Modeling to Describe the CYP2D6 Activity Score-Dependent Metabolism of Paroxetine, Atomoxetine and Risperidone	Rüdesheim et al.	2022	paroxetine	D/Di/GI	n.a. (only DGI, no DDI)	PK-Sim (version 10)	whole body	no	middle out (4)	local (1)	10 studies	internal + external (4)	> 10 studies, > 2 doses, 2 formulations (4)	internal and external; 3 studies (2)	15	n.a.	extensive
Prediction of maternal pharmacokinetics using physiologically based pharmacokinetic models: assessing the impact of the longitudinal changes in the activity of CYP1A2, CYP2D6 and CYP3A4 enzymes during pregnancy	Abduljalil et al.	2020	paroxetine	pregnancy	n.a.	SimCyp (version 19)	whole body	no	bottom up (6)	no (0)	4 studies	internal + external (4)	< 5 studies, > 2 doses, 1 formulation (1)	external; 3 studies (2)	13	base model: SimCyp compound file; assessment refers only to the model built upon the Simcyp compound file; the compound file itself was not evaluated (no information available); the compound file itself was not evaluated	extensive
Precision dosing based optimisation of paroxetine during pregnancy for poor and ultrarapid CYP2D6 metabolisers: a virtual clinical trial pharmacokinetics study.	Almurjan et al.	2020	paroxetine	pregnancy (+ pharmacogenetics)	n.a.	SimCyp (version 17)	whole body	no	middle out (4)	no (0)	7 studies	internal + external (4)	> 5 studies <10 studies, 1 dose, 1 formulation (1)	pregnancy PBPK model (CYP2D6 Phenotype-Specific); external; 1 study (1) (Dose Optimisation Application Model: no validation)	10	n.a.	substantial
Characterization of transplacental transfer of paroxetine in perfused human placenta: development of a pharmacokinetic model to evaluate tapered dosing	Nagai et al.	2013	paroxetine	pregnancy	n.a.	n.a.	semiphysiological PBPK (in a broader sense)	no	middle out (4)	no (0)	1 study	external (5)	< 5 studies; > 2 doses; 1 formulation (1)	external; 1 study (1)	11	n.a.	substantial

Predicting drug-drug interactions: Application of physiologically based pharmacokinetic models under a systems biology approach	Yeo et al.	2013	paroxetine	DDI/GI	inhibitor (CYP2D6)	SimCyp (version n.a.)	whole body	no	middle out (4)	no (0)	2 studies	internal + external (4)	< 5 studies; 2 doses; 1 formulation (1)	external; 1 study (1)	10	n.a.	substantial
Identification of cytochrome P450 isoforms involved in the metabolism of paroxetine and estimation of their importance for human paroxetine metabolism using a population-based simulator	Jornil et al.	2009	paroxetine	DDI/GI	n.a. (only DGI, no DDI)	SimCyp (version 9.10)	not clearly reported (paper refers to a generic Simcyp PBPK model, but the specific structural implementation (full whole-body vs. minimal/simplified PBPK) is not reported)	no	predominantly bottom up (6)	no (0)	extended model; 2 studies	internal + external (4)	< 5 studies; 1 dose; 1 formulation (0)	internal and external; 2 studies (2)	12	base model: SimCyp compound file; Assessment refers only to the model built upon the Simcyp compound file (extended model); the compound file itself was not evaluated (no information available)	substantial
Physiologically-Based Pharmacokinetic Modeling for the Prediction of CYP2D6-Mediated Gene-Drug Interactions	Storelli et al.	2019	paroxetine	DDI/GI	inhibitor (CYP2D6)	SimCyp (version 17)	minimal PBPK	no	middle out (4)	local (1)	9 studies (PK validation: 1, DDI validation: 7, DDGI validation: 1)	internal + external (4)	> 5 studies < 10 studies, > 2 doses, 1 formulation (2)	internal; 1 study (1)	12	base model: SimCyp compound file; assessment refers only to the model built upon the Simcyp compound file; the compound file itself was not evaluated (no information available)	substantial
The application of precision dosing in the use of sertraline throughout pregnancy for poor and ultrarapid metabolizer CYP 2C19 subjects: A virtual clinical trial pharmacokinetics study	Almurjan et al.	2021	sertraline	pregnancy (+ pharmacogenetics)	n.a.	SimCyp (version 17)	whole body	no	middle out (4) (base model: Templetton (2016); middle out; extended model: middle out)	global (3)	7 studies (base model: Templetton (2016); 4 studies; extended model: 3 studies)	internal + external (4) (base model: Templetton (2016); internal and external; extended model: external)	> 5 studies < 10 studies, > 2 doses, 1 formulation (2)	no validation (0)	13	n.a.	extensive
Utilizing Physiologically Based Pharmacokinetic Models to Support Rational Medication in Chinese Elderly Population	Wu et al.	2025	sertraline	geriatric (+ ethnicity)	n.a.	GastroPlus (version 9.8.2)	whole body	no	middle out (4) (the "verify & optimize" step is described generically; drug-specific optimisation details are not reported for sertraline)	no (0)	2 studies	internal (2)	< 5 studies, < 2 doses, 1 formulation (0)	no (0)	6	n.a.	intermediate
Generic Workflow to Predict Medicine Concentrations in Human Milk Using Physiologically-Based Pharmacokinetic (PBPK) Modelling: A Contribution from the ConcoPTION Project	Nauwelaerts et al.	2023	sertraline	lactation	n.a.	PK-Sim and MoBi (version 9.1)	whole body	no	middle out (4)	no (0)	21 studies (18 external, 3 internal)	internal + external (4)	> 10 studies, > 2 doses, 2 formulations (4)	external; 11 studies (2)	14	n.a.	extensive
Quantification of sertraline maternal/fetal ratio and amniotic fluid concentration using a pregnancy physiologically based pharmacokinetic model	Larley et al.	2023	sertraline	pregnancy	n.a.	RStudio (version 1.4.1717) + mrgsolve package (version 0.8.12)	minimal PBPK	no	middle out (base model: George (2020); middle out; extended model: Larley: middle out) (4)	local (1)	9 studies (base model: George (2020); 2 studies; extended model: Larley et al.: 7 studies)	internal + external (4)	> 5 studies < 10 studies, > 2 doses, 1 formulation (2)	internal + external; 7 studies (2)	13	n.a.	extensive
Application of physiologically based pharmacokinetic modeling for sertraline dosing recommendations in pregnancy	George et al.	2020	sertraline	pregnancy	n.a.	R (+ mrgsolve package)	minimal PBPK	no	middle out (4)	local (1)	2 studies	internal + external (4)	< 5 studies; > 2 doses; 1 formulation (1)	external; 1 study (1)	11	n.a.	substantial
Prediction of drug-drug interactions between various antidepressants and eubiotics or boosted protease inhibitors using a physiologically based pharmacokinetic modelling approach	Siccardi et al.	2013	sertraline	DDI	victim (CYP2C9, CYP3A4, CYP2D6, CYP2C19, CYP2B6)	SimCyp (version 10.1)	full or simple PBPK model (note: simple PBPK likely represents a reduced PBPK structure analogous to a minimal PBPK framework; however, the exact structural implementation is not described sufficiently to allow definitive classification)	no	bottom up (6)	no (0)	n.a.	informal comparison based on DD1 ratios from regulatory sources (0) (note: 0 points because no formal validation framework or independent, predefined validation datasets are described, and all comparisons are limited to informal post hoc agreement of simulated and observed data)	n.a.	n.a.	6	base model: SimCyp compound file; assessment refers only to the model built upon the Simcyp compound file (extended model); the compound file itself was not evaluated (no information available)	intermediate
Prediction of Maternal and Fetal Exposure to Escitalopram, Sertraline, and Paroxetine by Combining Human Ex Vivo Placenta Perfusion Data and Physiologically Based Pharmacokinetic Modeling	Prieta et al.	2025	sertraline	pregnancy	n.a.	SimCyp (version 22)	whole body	no	middle out (4)	no (0)	13 studies	internal + external (4) (Nonpregnant Healthy Volunteer Base PBPK Model: separation between refinement studies and validation studies not clearly documented)	> 10 studies, > 2 doses, 1 formulation (3)	external; 2 studies (2)	13	n.a.	extensive
Quantitative Prediction of Drug-Drug Interactions Involving Inhibitory Metabolites in Drug Development: How Can Physiologically Based Pharmacokinetic Modeling Help?	Templeton et al.	2016	sertraline	DDI	inhibitor (CYP2D6, CYP3A4)	n.a. (most likely SimCyp)	whole body	yes	middle out (4)	no (0)	4 studies	internal + external (4)	< 5 studies; > 2 doses; 1 formulation (1)	internal and external; 2 studies (2)	11	n.a.	substantial
Estimation of brain receptor occupancy for trazodone immediate release and once a day formulations	Oggianu et al.	2022	trazodone	brain exposure/ CNS targeting	n.a.	SimCyp (version 18.2)	whole body	no	middle out (4) (base model: Oggianu (2020); middle out; extended model: middle out)	local (1) (base model: Oggianu (2020); local; extended model: no)	base model: Oggianu (2020); 5 studies; extended model: 2 studies	internal + external (4) (base model: Oggianu (2020); internal and external; extended model: internal)	> 5 studies < 10 studies, > 2 doses, 2 formulations (3) (base model: Oggianu (2020); multiple doses; extended model: 1 dose)	no validation (0)	12	n.a.	substantial
Pharmacokinetics of duloxetine self-administered in overdose with quetiapine and other antipsychotic drugs in a Japanese patient admitted to hospital	Adachi et al.	2021	trazodone	toxicity/ drug overdose	n.a.	n.a.	minimal PBPK	no	middle out (4)	no (0)	1 study (case report with single adult overdose patient used for illustrative comparison only)	internal (2)	< 5 studies; 1 dose; 1 formulation (0)	internal validation; 1 study (1)	7	n.a.	intermediate
Precision dosing of venlafaxine during pregnancy: a pharmacokinetics modelling approach	Alemedi et al.	2023	venlafaxine	pregnancy (+ pharmacogenetics)	n.a.	SimCyp (version 20)	whole body	no	middle out (base model (Xue 2017); middle out; other development stages and final model; bottom-up) (4)	base model (Xue 2017); local (1)	13 studies (base model (Xue 2017); 2 studies; extended model: 11 studies)	internal + external (4)	> 10 studies, > 2 doses, > 2 formulations (4)	no (0)	13	n.a.	extensive

Utilizing Physiologically Based Pharmacokinetic Models to Support Rational Medication in Chinese Elderly Population	Wu et al.	2025	venlafaxine	geriatric (+ ethnicity)	n.a.	GastroPlus (version 9.8.2)	whole body	no	middle out (4) (the "verify & optimize" step is described generically; drug-specific optimization details are not reported for venlafaxine individually)	no (0)	1 study	internal (2)	< 5 studies, <2 doses, 1 formulation (0)	no (0)	6	n.a.	intermediate
Advancing inclusive healthcare through PBPK modelling: predicting the impact of CYP genotypes and enzyme ontologies on infant exposures of venlafaxine and its active metabolite O-desmethylenlafaxine in lactation	Pan et al.	2025	venlafaxine	lactation (+ pharmacogenetics)	n.a.	SimCyp (version 21)	whole body	yes	middle out (4)	local (1)	10 studies	internal + external (4)	> 10 studies, > 2 doses, >2 formulations (4)	internal; 2 studies (2)	15	n.a.	extensive
Prediction of basic drug exposure in milk using a lactation model algorithm integrated within a physiologically based pharmacokinetic model	Pansari et al.	2022	venlafaxine	lactation	n.a.	SimCyp (version 20)	minimal PBPK	no	middle out (4)	local (1)	4 studies	internal + external (4)	< 5 studies, > 2 doses, 2 formulations (2)	external; 2 studies (2)	13	n.a.	extensive
Prediction of Drug-Drug Interactions with Bupropion and Its Metabolites as CYP2D6 Inhibitors Using a Physiologically-Based Pharmacokinetic Model	Xue et al.	2017	venlafaxine	DDI	victim (CYP2D6)	SimCyp (version 15)	minimal PBPK	no	middle out (4)	no (0)	2 studies	internal + external (4) (Unclear whether both studies were external; therefore, internal + external validation was assumed)	< 5 studies, > 2 doses, 1 formulation (1)	external; 1 study (1)	10	n.a.	substantial
Prediction of drug-drug interactions between various antidepressants and efavirenz or boosted protease inhibitors using a physiologically based pharmacokinetic modelling approach.	Siccardi et al.	2013	venlafaxine	DDI	victim (CYP2D6, CYP2C19, CYP3A4, CYP2C8)	SimCyp (version 10.1)	full or simple PBPK model (note: simple PBPK likely represents a reduced PBPK structure analogous to a minimal PBPK framework; however, the exact structural implementation is not described sufficiently to allow definitive classification)	no	bottom up (6)	no (0)	n.a.	no validation of the extended model and the new application context was performed (0)	n.a.	n.a.	6	base model: SimCyp compound file; assessment refers only to the model built upon the Simcyp compound file (extended model); the compound file itself was not evaluated (no information available)	intermediate
Physiologically Based Pharmacokinetic Modeling for Substitutability Analysis of Venlafaxine Hydrochloride Extended-Release Formulations Using Different Release Mechanisms: Osmotic Pump Versus Openable Matrix	Lin et al.	2016	venlafaxine	drug formulation	n.a.	GastroPlus (version 8.6 00034)	semiphysiological PBPK	yes	middle out (4)	local (1) (additionally: 3-dimensional (3-D) PSA was conducted)	6 studies	internal (2)	> 5 studies < 10 studies; > 2 doses; > 2 formulations (3)	internal; 4 studies (2)	12	The 3-D PSA represents an extension of the local approach (two parameters varied simultaneously at fixed levels), rather than a formal global sensitivity analysis	substantial
Physiologically Based Pharmacokinetic Model of CYP2D6 Associated Interaction Between Venlafaxine and Strong Inhibitor Bupropion-The Influence of Age-Related Changes and Inhibitory Dose to Classify Therapeutic Success and Harm	Luecht et al.	2025	venlafaxine	DDI (+ geriatric)	victim (CYP2D6)	PK-Sim and MoBi (version 9.1)	whole body	yes	middle out (4)	no (0)	7 studies + data from KOBAS database (counted as 1 additional study)	internal (2)	> 5 studies < 10 studies, > 2 doses, 2 formulations (3)	DDI VEN + BUP: internal, 1 study (1) DDI VEN + BUP + ITRa: no	10	n.a.	substantial
Physiologically Based Pharmacokinetic Modeling to Unravel the Drug-gene Interactions of Venlafaxine: Based on Activity Score-dependent Metabolism by CYP2D6 and CYP2C19 Polymorphisms	Shen et al.	2024	venlafaxine, desvenlafaxine (metabolite)	D(D)GI	n.a. (only DGI, no DDI)	PK-Sim and MoBi (version 11.2)	whole body	yes	middle out (4)	local (1)	14 studies (base model: 9 studies (3 internal, 6 external); extended models: 5 studies)	internal + external (4)	> 10 studies, > 2 doses, >2 formulations (4)	internal; 1 study (1)	14	extended model = DGI models including CYP2D6, CYP2D6 + CYP2C19; final model: DGI model including CYP2D6 + CYP2C19	extensive
PBPK modeling to predict the pharmacokinetics of venlafaxine and its active metabolite in different CYP2D6 genotypes and drug-drug interactions with clarithromycin and paracetamol	Cho et al.	2024	venlafaxine, desvenlafaxine (metabolite)	D(D)GI	victim (CYP2D6)	PK-Sim (version 11.2)	whole body	yes	middle out (4)	local (1)	12 studies	internal + external (4) (12 studies; only 1 study for external validation)	> 10 studies, > 2 doses, 1 formulation (3)	internal; 1 study (1)	13	n.a.	extensive