Drug Design, Development and Therapy

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ORIGINAL RESEARCH

Utilizing Physiologically Based Pharmacokinetic Models to Support Rational Medication in Chinese Elderly Population

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Background: China is undergoing a pronounced shift towards an aging society, wherein the elderly constitute a prominent demographic relying significantly on medications. The imperative of administering rational medication to the elderly has gained considerable importance and warrants focused attention. The availability of pharmacokinetic (PK) data specific to the elderly is paramount for supporting informed medication practices. Unfortunately, studies addressing PK in the elderly are both infrequent and intricate, contributing to a lack of crucial data essential for tailoring personalized and rational medication approaches.

Methods: This study aimed to address this deficiency by employing the Physiologically Based Pharmacokinetic (PBPK) model, with the goal of supplying critical data to support rational medication strategies for the elderly. Additionally, we extended the application of PBPK models to Therapeutic Drug Monitoring (TDM) through the examination of four neuropsychiatric drugs.

Results: The PBPK models for 50 drugs in young and middle-aged Chinese adults were validated using clinical trial data. Simulated concentration–time curves closely matched the observed data, with C_{max} and AUC ratios within 0.5–2.0. For Chinese elderly, PBPK models for four drugs (ticagrelor, rivaroxaban, alprazolam, midazolam) showed strong agreement with observed data. Comparing PK profiles of 50 drugs, no significant differences were found between elderly and younger adults. Dosage recommendations for four neuropsychiatric drugs in the elderly were provided based on simulation results, ensuring therapeutic effectiveness and safety.

Conclusion: In conclusion, PBPK models for 50 commonly prescribed drugs within the Chinese elderly population were developed, tackling general data gaps associated with these specific medications. Medication plans were developed specifically tailored for the elderly population, presenting an alternative methodology and perspective for the implementation of individualized and rational medication practices.

Keywords: the elderly, pharmacokinetics, rational medication, individualized medicine, PBPK model

Introduction

In the past decades, there has been a remarkable increase in the elderly population (age >65 years), accounting for over 60% of the total prescriptions dispensed.[1] The aging process in the elderly often leads to the gradual decline of the function of multiple organs and systems, subsequently resulting in alterations in absorption, distribution, metabolism, and excretion (ADME) of drugs. These changes may ultimately translate into significant variations both in the efficacy and safety among the elderly population.[2] Concurrently, the risk associated with medication use among the elderly has been steadily increasing, due to an upsurge in polypharmacy and adverse drug reactions. Notably, China has entered an era of an aging society, with the population aged 60 years and above numbering approximately 264 million, accounting for 18.70% of the total population based on the data from the 7th China Population Census in 2021.[3] Confronted with this huge shift in population demographics, the clinical management of medication for the elderly in China encounters great challenges predominantly marked by the absence of evidence-based practices.

Received: 2 December 2024
Accepted: 4 April 2025
Published: 22 April 2025

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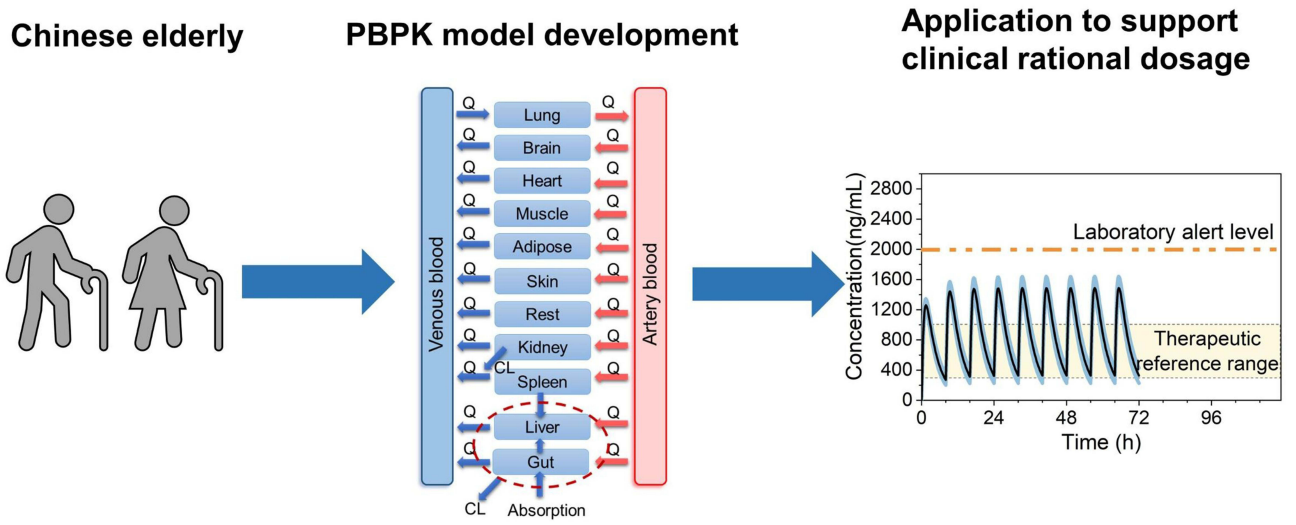
Graphical Abstract



Rational drug use seeks to establish the most appropriate treatment and dosage regimen to achieve maximum efficacy with minimal side effects for patients.[4] However, the challenge of rational drug use in the elderly population represents a significant hurdle worldwide. There are many factors contributing to this outcome, among which is the absence of pharmacokinetic data for drugs in the elderly population due to ethical and methodological challenges in clinical research, which could serve as a valuable reference for their medication management.[5] The situation was particularly pronounced in China. Our research team conducted a preliminary analysis of 31,311 drug package inserts in the Chinese pharmaceutical domain. The investigation revealed that, among the drugs surveyed, only 22.4% provided explicit labeling of information relevant to the elderly population. Furthermore, the elderly demographic exhibited an astonishing 80% deficit in pertinent pharmacokinetic data. In contrast, comprehensive data were available for majority of drugs in the young and middle-aged population in China. As a matter of fact, dosing regimens for elderly patients are usually extrapolated from those used for adult patients or adjusted based on adult dosing.[6] Additionally, in traditional clinical treatment, physicians typically formulate treatment plans following evidence-based medicine and clinical guidelines, subsequently modify the dosage and usage based on individual patient responses to treatment. However, this trial-and-error approach cannot predict efficacy and tolerability before administration, resulting in delayed dose adjustment and increasing the risks and costs associated with patient treatment. In light of this, applying innovative methods to elucidate the in vivo disposal and interaction patterns of frequently used drugs in the elderly, so as to develop more scientific medication plans, is the fundamental solution to rational clinical medication in the elderly population.

In recent years, physiologically based pharmacokinetic (PBPK) modeling[7] has emerged as a promising approach for evaluating drug exposure and obtaining mechanistic insight into drug characteristics. This is accomplished by integrating drug and system parameters into a dynamically interconnected model. PBPK modeling has been widely used in drug development, including dose selection for first-in-human trials, investigation of drug–drug interaction, assessment of food effect, and extrapolation of pharmacokinetics in special populations.[8]

In the present study, we developed PBPK models for 50 frequently prescribed drugs in the Chinese elderly population and then addressed existing data deficiencies pertaining to these specific drugs. We designed and conducted the study aiming to identify potential disparities in the PK characteristics of these drugs between the elderly and young or middle-aged populations, to provide an alternative approach for therapeutic drug monitoring (TDM), and thus supply essential data support to facilitate the rational use of medications within the elderly population in China.

Materials and Methods

The experimental design and technical roadmap of this study are depicted in Figure 1.

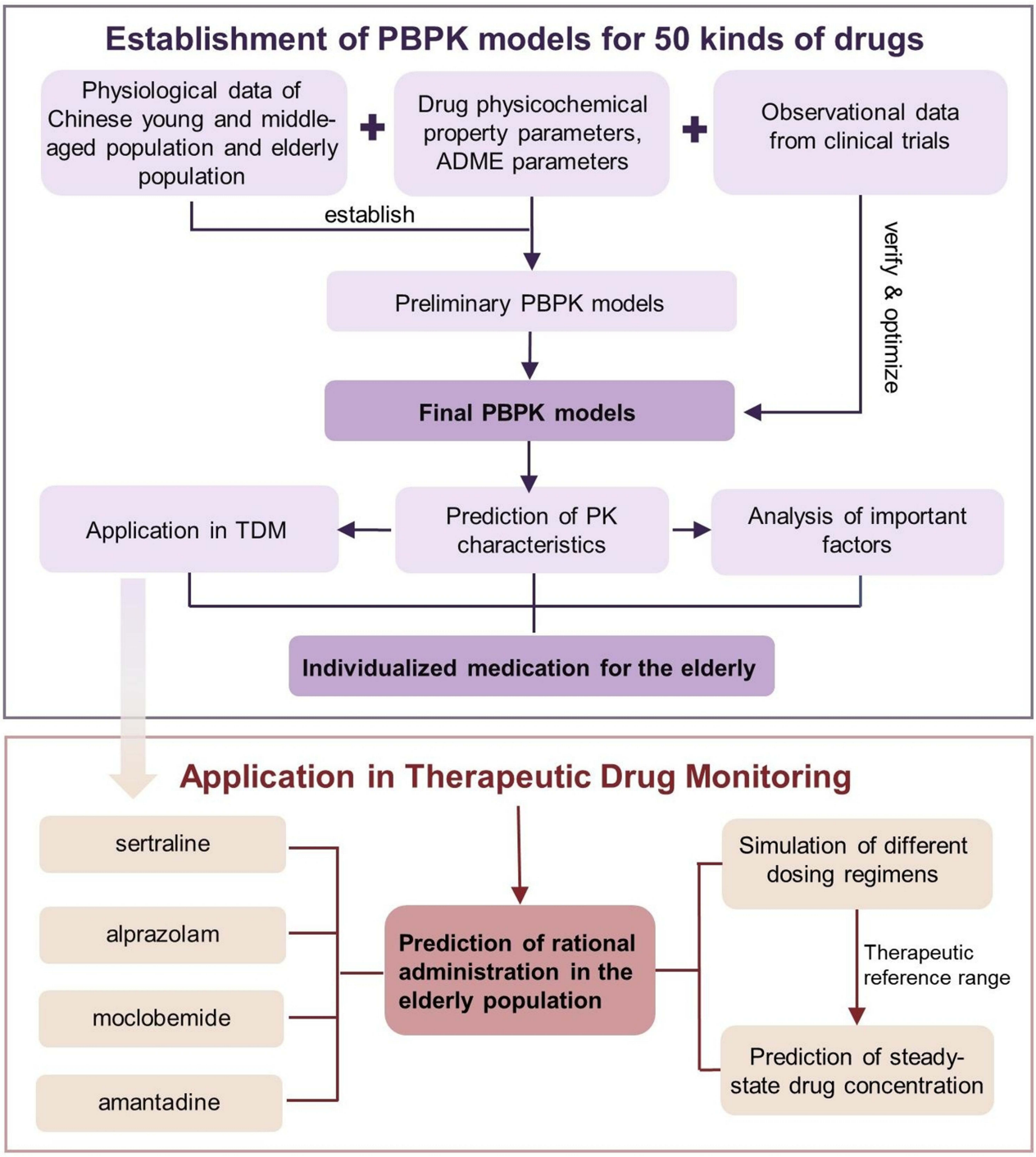


Figure 1 The technical roadmap.

Drug Selection, Data Collection, and Ethics

Drug Selection

In the present study, a total of 50 drugs that were frequently prescribed for the treatment of various prevalent diseases among elderly individuals in China were selected for PBPK modeling. The drug selection was guided by data provided by Beijing Institute of Geriatrics, National Health Commission, and Peking Union Medical College Hospital. Additionally, we consulted the "American Geriatrics Society Beers Criteria® for potentially inappropriate medication

https://doi.org/10.2147/DDDT.S501143

(PMI) use in older adults",[9] as well as the published "criteria of PMI for older adults in China".[10] Among the 50 drugs under investigation, there were 9 cardiovascular drugs, 24 psychiatric drugs, 3 drugs targeting gastrointestinal and digestive diseases, 5 anti-tumor drugs, 6 anti-infective drugs, and 6 other medications. The drug list is shown in Table 1.

Data Collection

Considering that oral administration represented the most widely accepted and convenient dosing route, the majority of the 50 drugs examined in this study were oral immediate-release formulations. There were only two exceptions, namely vancomycin, and imipenem, which were administered intravenously. Drug-related data including physicochemical properties, ADME parameters, and clinical PK data were acquired by searching DrugBank and PubMed database. The sources of these data[11–90, 91–145] were listed in Table 2. The visualization of published plasma concentration data was accomplished using GetData Graph Digitizer

Table 1 List of 50 Drugs Commonly Used in the Chinese Elderly to Establish PBPK Model

Drug Type	Drugs
Anticoagulant drugs	Warfarin, clopidogrel, ticagrelor, rivaroxaban
Antibiotics	Voriconazole, fluconazole, clarithromycin, vancomycin, imipenem, linezolid
Antidepressant drugs	Citalopram, venlafaxine, sertraline, paroxetine, amitriptyline, doxepin, desipramine, fluvoxamine, moclobemide, nortriptyline, fluoxetine
Antipsychotic drugs	Aripiprazole, amisulpride, risperidone
Sedative hypnotics	Alprazolam, midazolam, diazepam
Anti-Parkinson drugs	Amantadine, pramipexole
Antiepileptic drugs	Levetiracetam and lamotrigine
Antineoplastics	Tamoxifen, imatinib, apatinib, gefitinib, dasatinib
Hypolipidemic drugs	Atorvastatin, rosuvastatin, simvastatin, fluvastatin
Proton pump inhibitors	Omeprazole, ilaprazole, lansoprazole
Analgesic drugs	Tramadol, ketoprofen
Anti-arrhythmia agent	Metoprolol
Immunosuppressive drugs	Tramadol, ketoprofen
Antiemetic drugs	Ondansetron
Smoking cessation drugs	Varenicline

Table 2 Data Sources for 50 Drugs

Drugs	Drug Physicochemical Properties and ADME Parameters	Clinical Data of Chinese Adult Population	Clinical PK Data of Chinese Elderly Population
Warfarin	Drugbank; reference[11]	Reference[12]	
Clopidogrel	Internal data; reference[13–20]	Internal data	
Ticagrelor	Drugbank; reference[21–23]	Reference[24]	Reference[25]
Rivaroxaban	Drugbank; reference[26,27]	Reference[28]	Reference[29]
Voriconazole	Drugbank; reference[30,31]	Reference[32]	
Fluconazole	Drugbank; reference[33,34]	Reference[35]	
Clarithromycin	Drugbank; reference[36,37]	Reference[38,39]	
Vancomycin	Drugbank; reference[40–42]	Reference[43]	
Imipenem	Drugbank; reference[44]	Reference[45,46]	
Linezolid	Drugbank; reference[47–49]	Reference[50]	

(*Continued*)

Table 2 (Continued).

Drugs	Drug Physicochemical Properties and ADME Parameters	Clinical Data of Chinese Adult Population	Clinical PK Data of Chinese Elderly Population
Citalopram	Drugbank; reference[51,52]	Reference[53,54]	
Venlafaxine	Drugbank	Reference[55]	
Sertraline	Drugbank; reference[56,57]	Reference[58,59]	
Paroxetine	Drugbank; reference[60]	Reference[61]	
Amitriptyline	Drugbank; reference[62]	Reference[63,64]	
Doxepin	Drugbank	Reference[65]	
Desipramine	Drugbank; reference[66,67]	Reference[68]	
Fluvoxamine	Drugbank; reference[69,70]	Reference[71,72]	
Moclobemide	Drugbank; reference[70]	Reference[73,74]	
Nortriptyline	Drugbank; reference[75]	Reference[76]	
Fluoxetine	Drugbank; reference[77]	Reference[78,79]	
Amisulpride	Drugbank; reference[80,81]	Reference[82]	
Aripiprazole	Drugbank; reference[83,84]	Reference[85]	
Alprazolam	Drugbank; reference[86,87]	Reference[88]	Reference[89]
Risperidone	Drugbank; reference[90]	Reference[91,92]	
Midazolam	Drugbank	Internal data	Internal data
Diazepam	Drugbank; reference[93]	Reference[94]	
Amantadine	Drugbank	Reference[95,96]	
Pramipexole	Drugbank; reference[97,98]	Reference[99]	
Levetiracetam	Drugbank; reference[100]	Reference[101,102]	
Lamotrigine	Drugbank; reference[103]	Reference[104]	
Tamoxifen	Drugbank; reference[105]	Reference[106]	
Imatinib	Drugbank; reference[107]	Reference[108,109]	
Apatinib	Drugbank; reference[110,111]	Reference[111,112]	
Gefitinib	Drugbank; reference[113]	Reference[114]	
Dasatinib	Drugbank; reference[115]	Reference[116]	
Atorvastatin	Drugbank; reference[117]	Reference[118]	
Rosuvastatin	Drugbank; reference[119]	Reference[120]	
Simvastatin	Drugbank; reference[121,122]	Reference[123]	
Fluvastatin	Drugbank; reference[121]	Reference[124]	
Omeprazole	Drugbank; reference[125,126]	Reference[127]	
Ilaprazole	Drugbank; reference;[128] internal data	Internal data	

(*Continued*)

https://doi.org/10.2147/DDDT.S501143

Table 2 (Continued).

Drugs	Drug Physicochemical Properties and ADME Parameters	Clinical Data of Chinese Adult Population	Clinical PK Data of Chinese Elderly Population
Lansoprazole	Drugbank; reference[129–131]	Reference[132]	
Tramadol	Drugbank; reference	Reference[133–135]	
Ketoprofen	Drugbank	Reference[136]	
Metoprolol	Drugbank	Reference[137]	
Tacrolimus	Drugbank; reference[138]	Reference[139]	
Ciclosporin	Drugbank; reference[140–142]	Reference[143]	
Ondansetron	Drugbank; reference[144]	Reference[145]	
Varenicline	Drugbank	Reference[144]	

(version 2.22, S. Fedorov) software. Noncompartmental analysis (NCA) was applied to calculate PK parameters. In this study, clinical PK data for 50 drugs in Chinese young or middle-aged population (age 18–45 years) and elderly population (age 65–80 years) were retrieved and analyzed. Nevertheless, due to the limited number of clinical trials conducted within the Chinese elderly, PK data were accessible only for ticagrelor, rivaroxaban, alprazolam, and midazolam in this demographic group.

Ethics

This study follows the Declaration of Helsinki and was approved by the Ethics Committee of Peking Union Medical College (Beijing, China) with an exemption from informed consent.

PBPK Model Development

PBPK models for 50 drugs in Chinese middle-aged and elderly populations were constructed using the Gastroplus software (version 9.8.2, Simulation Plus) in this study.

Virtual Population

The Population Estimates for Age-Related Physiology (PEAR) module in Gastroplus was used to generate virtual populations representing Chinese adult and the elderly. Briefly demographic data such as height, weight, and Body Mass Index (BMI) based on age were calculated using statistical formulas. Furthermore, systematic biology parameters of the population such as tissue blood flow, tissue volume, enzyme content, and glomerular filtration rate (GFR) were obtained from demographic data, with some variability being added. For the young or middle-aged population, in this current study it was defined as 18–45 years old, while for the elderly population, the age was set between 65 and 80 years old.

Model Construction

For each drug, the PBPK model divided the body into distinct compartments based on physiological and anatomical characteristics, including heart, brain, liver, kidneys, lungs, adipose tissue, muscle, gastrointestinal tract, skin, spleen, reproductive system, yellow and red bone marrow, and the remainder of the body. The Advanced compartmental absorption and transit (ACAT) model, a component of the Gastroplus software suite, was employed to simulate oral absorption.[146] The ACAT model was composed of nine compartments, including stomach, seven segments of small intestine and colon. Within each compartment, drugs could undergo various processes including disintegration, dissolution, degradation, precipitation, penetration, and metabolism. Moreover, the drugs had the ability to move into the subsequent compartment to engage in the process mentioned above. Additionally, essential physiological parameters of the gastrointestinal tract, including luminal fluid volume, blood flow, gastric emptying-rate, pH value within each compartment, and dietary status, were accessed through an integrated database within the Gastroplus software platform.

In this study, all compartments in the PBPK model were considered well stirred, with each being defined by tissue blood flow, tissue volume, and tissue-plasma partition coefficient (K_p). The K_p calculation methods utilized in Gastroplus include Poulin&Theil,[147] Berezhkovskiy,[148] Rodgers and Rowland,[105,107] Lukacova (Rodgers & Single) and Lukacova with Lysosomes. The Lukacova (Rodgers & Single) method was used for the majority of the drugs in this study. Nevertheless, when dealing with alkaline drugs with a logP greater than 2 and a pKa between 6.5 and 11, the Lukacova with Lysosomes method emerged as the preferred choice, given their tendency to undergo lysosomal capture. Systematic clearance (CL) was derived from literature or database. When a drug was metabolized through cytochrome 450 (CYP450) enzyme, the relevant parameters (V_{max}, K_m) were incorporated into the elimination profile of the drug.

For the 2 intravenous infusion drug models, there was no need to consider the processes of drug dissolution and absorption in the gastrointestinal tract. As for the elimination process of the drug in the body, the model construction methods for intravenous and oral formulations were consistent.

Model Validation

For each drug, the PBPK model was validated by comparing the simulated PK profiles with the observed profiles from the same clinical trial design, including route of administration, dose regimen, and study duration. The ratios of simulated to observed PK parameters (C_{max} and AUC) were calculated, and a range of 0.5–2 times[149] was considered accepted. For some drugs, more than one set of observed clinical data was collected. The C_{max} and AUC of each set of observed clinical data were compared separately with the predicted values. It was noted that comprehensive PK data were available only for four drugs (ticagrelor, rivaroxaban, alprazolam, midazolam) in the elderly, due to the scarcity of clinical trials conducted within this population in China. Consequently, the PBPK models for the remaining 46 drugs were solely validated using data from Chinese young or middle-aged population.

Model Application

Comparison of Pharmacokinetics of 50 Drugs Between Chinese Elderly and Young or Middle-Aged Populations

For each drug, the model simulations were carried out for Chinese elderly and young or middle-aged populations, following the clinical recommendations for usage and dosage, sourced from "UpToDate"[150] and the information provided in the package inserts. Each simulation involved 50 virtual subjects with a female proportion of 50%. The potential differences between the two populations were assessed by comparing the simulated data, including drug exposure (AUC and C_{max}), as well as the plasma concentration–time profiles.

Application to Support Clinical Rational Dosage for Neuropsychiatric Drugs

Neuropsychiatric drugs often exhibit a narrow therapeutic range, substantial individual variability, suboptimal efficacy,[151] and a propensity to induce adverse central nervous system reactions, including sleep disturbances, hallucinations, and even life-threatening outcomes.[152–155] Therapeutic drug monitoring (TDM) is frequently applied to inform clinical rational administration of these drugs, thereby optimizing both efficacy and tolerance. In accordance with clinical guidelines presented in UpToDate, the application of TDM was recommended for neuropsychiatric medications, including sertraline, moclobemide, alprazolam, and amantadine, primarily due to their high-risk profiles in clinical medication management. The therapeutic reference and alert concentrations of these drugs are shown in Table 3. Of note, the usage and dosage for the elderly was not clearly demonstrated in the package inserts, or it was just mentioned that the drugs should be administered with caution or reduced as appropriate. In order to optimize the rational dosage for

Table 3 Therapy Reference Range and Laboratory Alert Level of 4 Drugs

Drug	Therapeutic Reference Range	Laboratory Alert Level
Sertraline	10~150 ng/mL	300 ng/mL
Alprazolam	5~50 ng/mL	100 ng/mL
Moclobemide	300~1000 ng/mL	2000 ng/mL
Amantadine	300~600 ng/mL	1200 ng/mL

https://doi.org/10.2147/DDDT.S501143

neuropsychiatric drugs, the established PBPK models for these 4 drugs were applied to simulate different drug administration scenarios in virtual 300 elderly subjects with female proportion of 50%. The recommended usage and dosage are depicted in Table 4.[152–155]

Results

Model Construction and Validation

Model Construction

The parameters for PBPK modeling were mainly obtained from the literature. For the missing information, the values were predicted using Gastroplus software. The input parameters are shown in Table 5.

Table 4 Administration Regimes of 4 Drugs for Simulation

Drug	Time	Regimen (a)	Regimen (b)	Regimen (c)	Regimen (d)	Regimen (e)
Sertraline	Day 1–10	25 mg qd	50 mg qd	100 mg qd	150 mg qd	200 mg qd
Alprazolam	Day 1–2	0.2 mg tid	0.2 mg tid	0.2 mg tid	0.2 mg tid	0.2 mg tid
	Day 3–4	0.2 mg tid	0.4 mg tid	0.4 mg tid	0.4 mg tid	
	Day 5–6	0.2 mg tid	0.4 mg tid	0.6 mg tid	0.6 mg tid	
	Day 7	0.2 mg tid	0.4 mg tid	0.6 mg tid	0.8 mg tid	
Moclobemide	Day 1–3	50 mg tid	100 mg bid	100 mg tid	150 mg tid	300 mg bid
Amantadine	Day 1–14	50 mg qd	50 mg bid	100 mg qd	50 mg bid	200 mg bid
	Day 14–28	100 mg qd	50 mg bid	100 mg bid	100 mg bid	200 mg bid

Notes: (1) For sertraline, the recommended dosage for the treatment of depression with this medication was as follows: patients were advised to administrate 50 mg once a day, with a maximum allowable daily dose of up to 200 mg; (2) For alprazolam, an anti-anxiety medication, the typical dosage was 0.4 mg taken three times a day, with the option to dose escalation as needed, up to a maximum daily limit of 4 mg. Since the elderly individuals were more sensitive to this medication and should start with a lower dose of 0.2 mg (half a tablet) three times a day, gradually increasing the dose through titration to the maximum tolerated level; (3) For moclobemide, the therapeutic dosage for depression was 300–450 mg each day. This medication was advised to administer orally after meals, usually divided into 2 to 3 separate doses. In certain cases, it may be considered appropriate to titrate the dosage upwards to a maximum of 600 mg daily during the second week of treatment. It is essential to reduce dose appropriately when prescribing this medication to elderly patients; (4) For Amantadine, the general dosage for the treatment of both Parkinson's disease and Parkinson's syndrome was 100 mg administered once daily, with the option of 1–2 times daily dosing, and a maximum daily dosage not exceeding 400 mg. It was imperative to individualize the dosage according to medical guidance and the patient's specific clinical circumstances. In accordance with the medication data mentioned above, the simulated dose regimens were devised for these four drugs.
Abbreviations: qd, once daily; bid, twice daily; tid, three times a day.

Table 5 The Input Parameters for Modeling of 50 Drugs

Drug	mW (g/mol)	logPo:w	pKa	P_{eff} (10^{-4} cm/s)	fu_p	B:P ratio	Kp*	V_{ss}(L)	CL (L/h)
Warfarin	308.33	2.7	5.1	4	0.009	0.07	A	13.98	0.15
Clopidogrel	321.83	3.89	4.55	2.71	0.02	0.72	B	243.30	95.34
Ticagrelor	522.58	3.52	12.94; 2.28	1.79	1	0.65	B	100.39	13.06
Rivaroxaban	435.88	1.5	2.28; 12.94	2.5	0.05	0.71	C	36.08	8.22
Voriconazole	349.32	1.8	2.27; 12.71	2.71	0.42	0.78	A	72.70	13.06
Fluconazole	306.28	0.5	2.56	3	0.9	0.83	C	40.44	0.99
Clarithromycin	747.97	3.16	8.99	39.7	0.3	1.23	C	171.87	27.89
Vancomycin	1449.3	2.45	2.18; 7.75	0.07	0.15	0.55	C	36.96	8.46
Imipenem	299.35	−3.9	8.99	0.45	0.8	1.8	C	29.29	26.27
Linezolid	337.35	0.232	1.7	3.22	0.69	2.5	C	29.28	6.48

(*Continued*)

Table 5 (Continued).

Drug	mW (g/mol)	logPo:w	pKa	P_{eff} (10^{-4} cm/s)	fu_p	B:P ratio	Kp*	V_{ss}(L)	CL (L/h)
Citalopram	324.4	3.76	9.78	0.6	0.2	1.6	A	893.97	6.77
Venlafaxine	277.41	2.69	14.42; 8.91	0.6	0.7	1.2	A	271.92	34.25
Sertraline	306.24	5.51	8.99	1.61	0.016	1.5	A	884.69	25.00
Paroxetine	329.37	3.55	9.66	0.9	0.5	1.26	B	535.71	16.50
Amitriptyline	277.41	4.92	9.4	0.2305	0.05	1.04	A	633.15	25.05
Doxepin	279.38	4.29	8.96	0.45	0.35	1.08	A	1341.80	64.27
Desipramine	266.39	4.45	10.32	0.454	0.15	1.2	B	500.56	8.60
Fluvoxamine	318.34	4	9.16	0.27	0.25	3.5	B	1025.02	62.92
Moclobemide	268.74	1.79	10.6; 6.2	2.5	0.5	3.5	B	69.45	20.94
Nortriptyline	263.38	4.39	10.1	0.8298	0.07	1.71	B	1199.48	40.15
Fluoxetine	309.33	5.5	9.82	0.38	0.06	2.38	B	1204.77	15.72
Amisulpride	369.49	0.16	9.37	0.4	0.84	0.5	B	146.56	17.00
Aripiprazole	448.4	3.9	7.6	3.12	0.02	0.65	A	173.15	2.05
Alprazolam	308.77	2.12	2.4	2	0.29	0.78	B	48.78	4.62
Risperidone	410.49	3.04	3.11; 8.24	2	0.135	0.74	A	122.26	3.15
Midazolam	325.77	2.7	5.95;0.84	4.33	0.04	0.55	A	61.06	19.65
Diazepam	284.74	2.82	3.4	12.434	0.03	0.5	C	125.68	1.11
Amantadine	151.25	2.44	10.71	1.5	0.37	1.6	A	403.44	12.99
Pramipexole	211.3	1.42	10.31; 17.66	1	0.85	1.7	A	477.14	24
Levetiracetam	170.21	−0.64	16.09; −1.6	2.5	0.996	1.1	B	146.56	3.84
Lamotrigine	256.1	1.93	5.5	2.2	0.45	1	B	72.98	1.14
Tamoxifen	371.53	5	8.76	0.45	0.001	0.6	B	165.02	0.05
Imatinib	493.62	4.38	12.69; 7.84	0.5	0.5	0.73	A	174.47	10.00
Apatinib	397.48	3.14	15.23; 5.41	0.8	0.076	0.995	B	206.61	43.07
Gefitinib	446.91	4.1	5.4; 7.2	0.77	0.089	1.8	B	1063.55	32
Dasatinib	488.01	3.2	10.99; 7.2	1.3	0.05	1.8	C	388.652	72.15
Atorvastatin	558.65	5.7	4.46	1.47	0.05	0.61	C	359.98	43.87
Rosuvastatin	481.55	−0.33	4.76	0.08	0.115	0.67	C	19.66	17.50
Simvastatin	418.58	4.68	−2.8;14.91	4.28	0.012	0.56	C	475.94	40.00
Fluvastatin	411.48	4.5	−2.8;4.54	1.65	0.015	0.57	A	9.73	26.00
Omeprazole	345.42	2.23	8.7; 4.4	0.67	0.04	0.59	C	7.33	62.92
Ilaprazole	366.44	4	10.1; 4.27	4.25	0.045	0.5	A	19.61	5.50

(*Continued*)

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Table 5 (Continued).

Drug	mW (g/mol)	logPo:w	pKa	P_{eff} (10^{-4} cm/s)	fu_p	B:P ratio	Kp*	V_{ss}(L)	CL (L/h)
Lansoprazole	369.37	1.9	4.15	0.4	0.029	0.59	C	27.34	13.09
Tramadol	263.38	2.71	9.41	5	0.80	1.07	A	170.99	62.92
Ketoprofen	254.29	3.12	9.16	1.3	1	0.59	B	4.96	3.84
Metoprolol	267.37	−1.72	9.39	1.34	0.11	0.86	A	152.13	36.30
Tacrolimus	804.04	3.3	9.95; 2.94	2.16	1	2	C	80.2	13.69
Ciclosporin	1202.6	3.25	13.23	19.75	0.1	0.73	C	262.88	15.03
Ondansetron	293.37	2.4	7.34; 16.13	0.72	0.02	0.65	A	35.62	35.62
Varenicline	211.27	0.8	9.73; 1.82; −2.88	1.25	0.8	1	A	121.27	7.36

Notes: *Kp calculated method: A: Lukacova (Rodgers & Single); B: Lukacova with Lysosomes; C: Poulin & Theil.

Model Validation

For the young or middle-aged Chinese adults (age 18–40 years of old), the models of 50 drugs were validated using the observed data from clinical trials, including PK profiles and parameters (AUC and C_{max}). Among most of the 50 drugs, the simulated concentration–time curves closely matched the observed, whether in the absorption or elimination phase, with clinical observations evenly distributed along the mean simulated curves or within 90% confidence intervals (Figure 2). Furthermore, the simulated PK parameters ($AUC_{0\text{-}t}$ and $C_{max)}$ demonstrated close alignment with the observed data, with C_{max} ratios ranging from 0.76 to 1.44 and AUC ratios ranging from 0.61 to 1.41 (Supplementary Table 1), falling within the predefined range of 0.5–2.0.

For the Chinese elderly, PBPK models were solely validated for 4 drugs (ticagrelor, rivaroxaban, alprazolam, and midazolam), because comprehensive PK data were available only for these 4 drugs in the elderly. The results revealed a strong agreement between the simulated and the observed data, with ratios of AUC and C_{max} falling within the range of 0.89 to 1.09 (Supplementary Figure 1 and Supplementary Table 2).

Comparing of PK Profiles of 50 Drugs in Chinese Elderly and Young or Middle-Aged Populations

Scaling the age-dependent parameters according to the software's built-in algorithm, we constructed a cohort of elderly people (50% women) aged 65–80 years. The mean PK characteristics of the elderly are shown in Figure 3. The mean pharmacokinetics of the elderly and adult are compared in Table 6. The results showed that there was no significant difference in PK parameters between the elderly population, with ratios consistently falling within the range of 0.81 to 1.29.

Application to Support Clinical Rational Dosage for Neuropsychiatric Drugs

The pharmacokinetic characteristics of four neuropsychoactive drugs (sertraline, alprazolam, moclobemide, and amantadine) in the elderly Chinese population were simulated using different dose regimens, and the results are shown in Figure 4.

Recommendation for Sertraline

The simulation results for sertraline (as depicted in Figure 4A) revealed that the mean steady-state plasma concentration (Css) in virtual elderly subjects did not entirely fall within the therapeutic reference range. Specifically, the trough concentrations were observed to fall below the lower limit of 10 ng/mL at the daily dose of 25 mg (Figure 4A-a). When the dose was increased to 50 mg (Figure 4A-b), the mean sertraline concentration was increased and managed to fall within the therapeutic reference range, but the trough concentration remained close to 10 ng/mL. In contrast, with dosing regimens of 100 mg (Figure 4A-c), 150 mg (Figure 4A-d), and 200 mg (Figure 4A-e), the C_{ss} in virtual elderly subjects

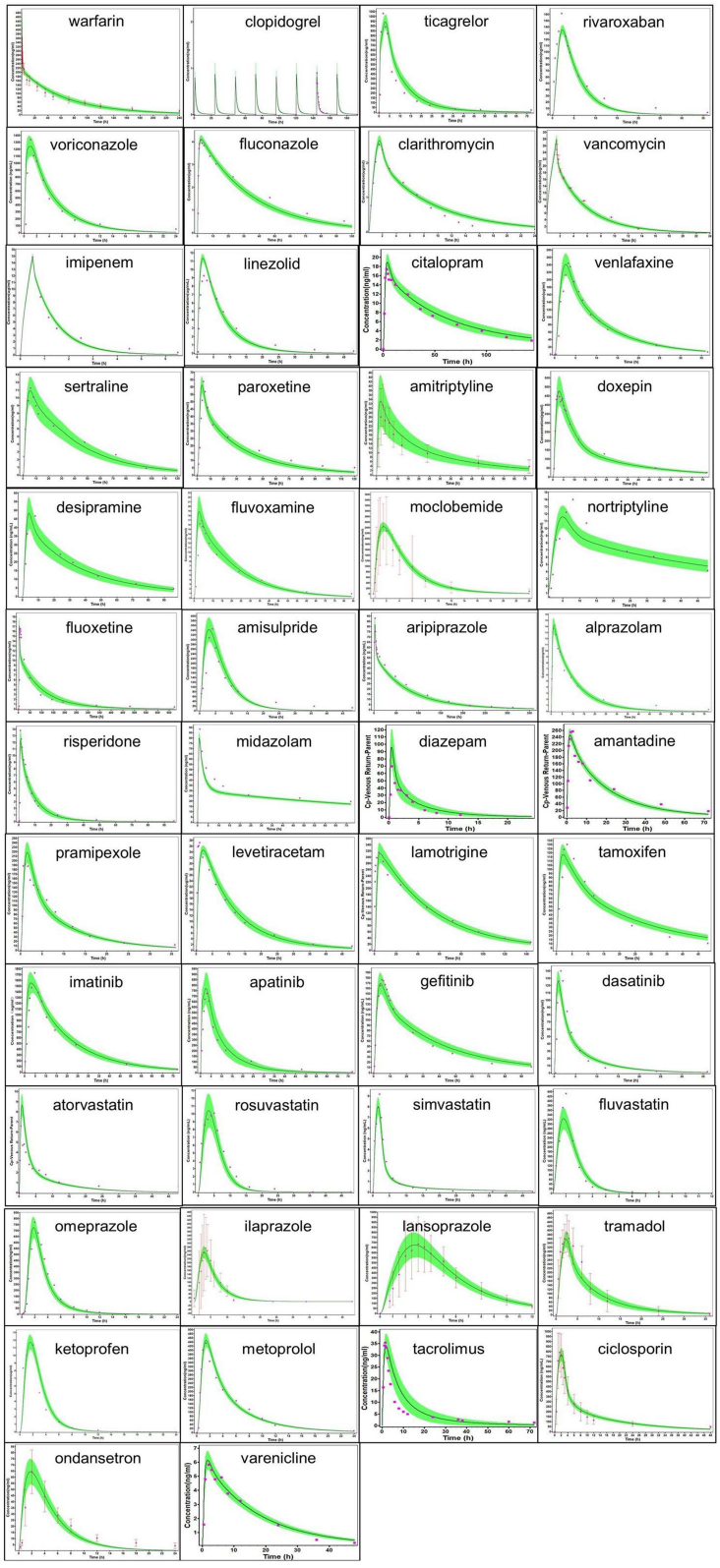

Figure 2 The simulated concentration–time curves of 50 drugs.

https://doi.org/10.2147/DDDT.S501143

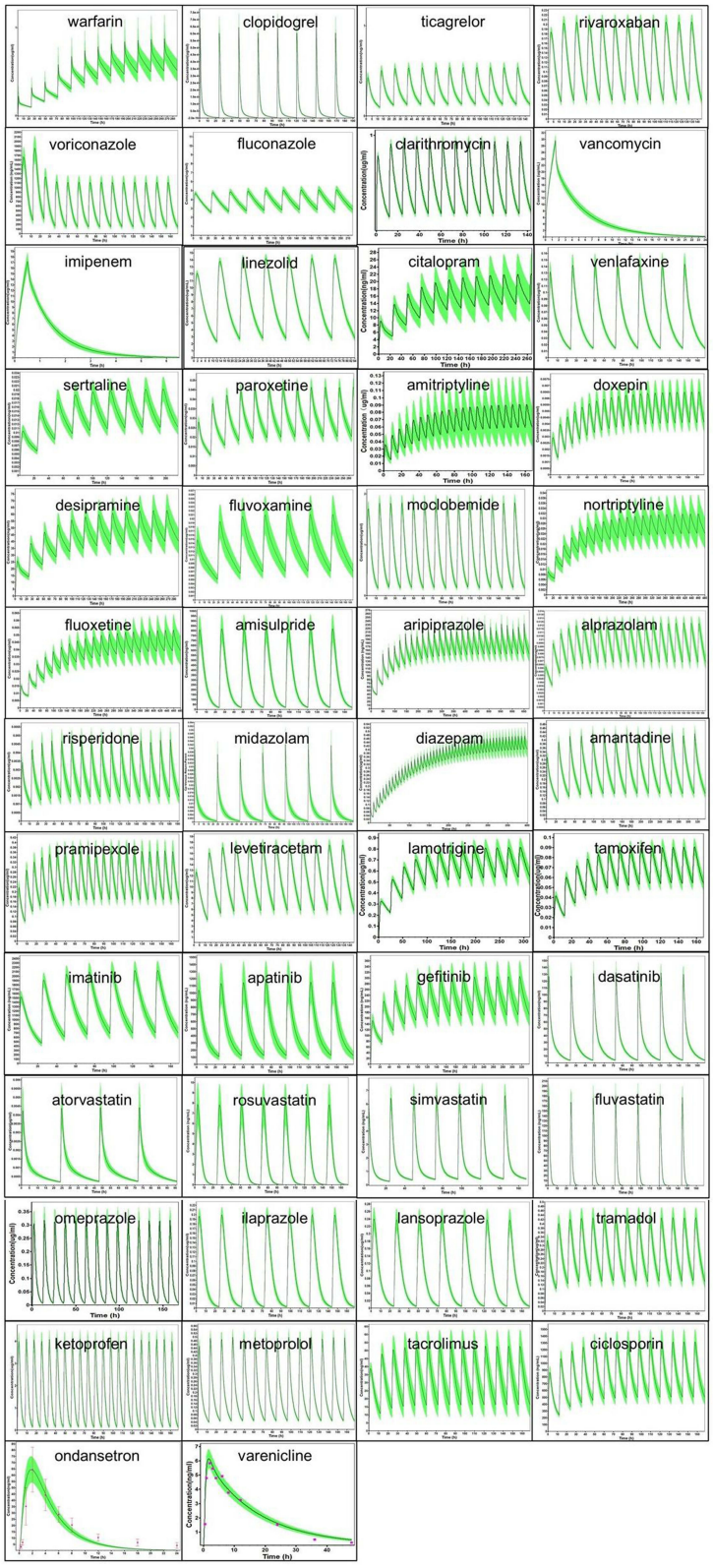

Figure 3 The mean PK characteristics of 50 drugs for the elderly.

Table 6 The Comparison of Mean Pharmacokinetics in the Elderly and the Young or Middle-Aged Population

Drug	Dose	Parameter	Adult Mean (90% CI)	Elderly Mean (90% CI)	Ratio (Elderly/Adult)
Warfarin	2.5mg qd	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	899.43(798.40–1000.40) 165.90(158.00–174.00)	846.39(797.40–895.40) 169.50(161.00–178.00)	0.94 1.02
Clopidogrel	75mg qd	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	0.80(0.70–0.89) 6.57(5.96–7.17)	0.79(0.69–0.87) 6.03(5.44–6.61)	0.99 0.92
Ticagrelor	90mg bid	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	1071.10(997.70–1144.50) 35.55(32.70–38.40)	996.71(937.20–1056.20) 35.90(33.40–38.40)	0.93 1.01
Rivaroxaban	15mg bid	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	140.22(134.50–146.00) 4281.50(3990.10–4573.00)	132.60(126.80–138.40) 3971.20(3691.60–4250.90)	0.95 0.93
Voriconazole	200mg bid	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	1888.20(1751.90–2024.60) 95.98(88.70–103.00)	2008.00(1850.60–2165.50) 99.60(91.00–108.00)	1.06 1.04
Fluconazole	200mg qd	C_{max} (ug/mL) AUC_{0-t} (ug*h/mL)	10.09(9.64–10.54) 2470.8(2317.80–2623.80)	10.25(9.82–10.67) 2493.30(2352.80–2633.90)	1.02 1.01
Clarithromycin	250mg bid	C_{max} (ug/mL) AUC_{0-t} (ug*h/mL)	1.45(1.37–1.52) 75.13(70.37–79.89)	1.47 (1.40–1.55) 76.57(71.73–81.41)	1.02 1.02
Vancomycin	1000mg	C_{max} (ug/mL) AUC_{0-t} (ug*h/mL)	27.26(26.42–28.10) 118.43(110.9–126.0)	29.13(28.28–29.98) 119.92(113.20–126.70)	1.07 1.01
Imipenem	500mg	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	24.03(23.17–24.88) 15.77(15.05–16.49)	25.92(24.88–26.96) 17.73(16.97–18.49)	1.08 1.12
Linezolid	600mg	C_{max} (ug/mL) AUC_{0-t} (ug*h/mL)	11.96(11.49–12.43) 553.42(518.40–588.50)	14.64(14.05–15.25) 633.94(594.10–673.80)	1.22 1.15
Citalopram	20mg qd	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	46.44(41.15–51.72) 10.73(9.49–12.00)	51.86(45.58–58.14) 12.07(10.60–13.50)	1.12 1.12
Venlafaxine	150mg qd	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	138.00(128.00–148.00) 9.07 (8.45–9.69)	163.00(151.00–174.00) 10.90 (10.00–12.00)	1.18 1.20
Sertraline	50mg qd	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	23.84(21.00–26.00) 5.60(4.99–6.21)	23.50(21.00–26.00) 5.51(4.81–6.21)	0.99 0.98
Paroxetine	20mg qd	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	53.92(49.53–58.31) 11.87(10.80–13.00)	53.50(49.44–57.55) 11.66(10.70–12.60)	0.99 0.98
Amitriptyline	25mg bid	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	40.20(34.00–47.00) 4.35(3.63–5.07)	44.45(37.00–51.00) 4.65(3.89–5.41)	1.11 1.07
Doxepin	25mg tid	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	5.13(4.60–5.66) 540.75(485.00–597.00)	4.15(3.91–5.10) 479.18(416.00–543.00)	0.81 0.89
Desipramine	50mg qd	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	134.00(117.5–150.6) 31.18(27.31–35.40)	115.78(103.80–127.70) 27.13(24.30–30.00)	0.86 0.87
Fluvoxamine	50mg qd	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	20.80(18.00–24.00) 2002.40(1729.00–2276.00)	18.64(16.00–21.00) 1702.80(1452.00–1954.00)	0.90 0.85
Moclobemide	200mg bid	C_{max} (ug/mL) AUC_{0-t} (ug*h/mL)	1.87 (1.78–1.97) 67.49(62.12–72.87)	1.90(1.80–2.01) 76.88(70.44–83.32)	1.02 1.14
Nortriptyline	25mg qd	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	36.69(31.00–42.00) 12.76(10.85–14.66)	36.94(33.00–41.00) 13.00(11.62–14.38)	1.01 1.02

(*Continued*)

https://doi.org/10.2147/DDDT.S501143

Table 6 (Continued).

Drug	Dose	Parameter	Adult Mean (90% CI)	Elderly Mean (90% CI)	Ratio (Elderly/Adult)
Fluoxetine	20mg qd	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	25.46(23.00–28.00) 4062.40(3702.00–4423.00)	24.43(22.00–27.00) 3837.00(3484.00–4190.00)	0.96 0.94
Amisulpride	400mg qd	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	731.69(659.00–804.40) 23.71(21.60–25.80)	709.47(604.00–815.00) 21.59(18.60–24.60)	0.97 0.91
Aripiprazole	10mg qd	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	238.00(223.00–253.10) 110.60(103.00–118.10)	249.63(231.10–268.20) 114.40(106.00–123.00)	1.05 1.03
Alprazolam	0.4mg tid	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	12.74(12.00–14.00) 1513.00 (1407.00–1620.00)	14.21(13.00–15.00) 1650.50(1538.00–1763.00)	0.90 0.92
Risperidone	1mg bid	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	10.70(10.00–11.00) 939.66(852.00–1028.00)	10.49(9.66–11.00) 1017.50(917.00–1118.00)	0.98 1.08
Midazolam	7.5mg qd	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	35.50(30.00–41.00) 178.50(144.26–212.74)	37.67(33.10–42.20) 230.74(190.93–270.56)	1.06 1.29
Diazepam	5mg tid	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	555.18(530.00–580.00) 147.70(141.80–153.60)	520.45(494.00–546.00) 139.00(132.90–145.10)	0.94 0.94
Amantadine	100mg bid	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	421.81(393.30–450.30) 77.47(71.70–83.30)	468.59(437.70–499.50) 89.95(82.90–97.00)	1.11 1.16
Pramipexole	125mg tid	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	398.80(364.00–433.60) 38.94(35.51–42.38)	393.54(367.40–419.60) 38.79(36.10–41.50)	0.99 1.00
Levetiracetam	500mg bid	C_{max} (ug/mL) AUC_{0-t} (ug*h/mL)	14.31(13.66–14.95) 832.13(787.00–877.20)	15.42(14.57–16.27) 862.52(807.60–917.50)	1.08 1.04
Lamotrigine	25mg qd	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	815.70(771.50–859.80) 202.90(192.10–213.60)	835.03(776.00–894.00) 208.44(194.10–222.80)	1.02 1.03
Tamoxifen	10mg bid	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	87.37(81.00–94.00) 10.35(9.57–11.13)	100.80(92.10–109.50) 11.50(10.51–12.48)	1.15 1.11
Imatinib	400mg qd	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	2460.50(2295.80–2625.10) 212.40(197.30–227.50)	2130.30(1939.90–2320.60) 199.00(181.60–216.50)	0.87 0.89
Apatinib	750mg qd	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	931.29(766.80–1095.80) 58.11(46.40–69.90)	1112.50(892.80–1332.20) 74.48(56.80–92.10)	1.19 1.28
Gefitinib	250mg qd	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	324.10(298.60–349.60) 72.21(65.99–78.43)	356.13(328.30–384.00) 76.81(70.30–83.30)	1.10 1.06
Dasatinib	100mg qd	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	140.59(128.50–152.70) 2912.50(2695.30–3129.70)	143.14(131.70–154.60) 2825.20(2559.40–3091.00)	1.02 0.97
Atorvastatin	10mg qd	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	5.14(4.59–5.69) 91.70(85.00–99.00)	4.91(4.50–5.32) 90.85(86.00–96.00)	0.96 0.99
Rosuvastatin	5mg qd	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	7.26(6.14–8.38) 308.22(265.20–351.20)	7.91(6.73–9.09) 324.04(273.10–375.00)	1.09 1.05
Simvastatin	20mg qd	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	7.79(7.10–8.49) 293.43(268.20–318.60)	8.21(7.36–9.05) 307.81(279.30–336.30)	1.05 1.05
Fluvastatin	20mg qd	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	181.34(163.70–198.90) 2416.70(2216.80–2616.60)	181.34(164.20–198.50) 2351.90(2159.20–2544.50)	1.00 0.97

(*Continued*)

Table 6 (Continued).

Drug	Dose	Parameter	Adult Mean (90% CI)	Elderly Mean (90% CI)	Ratio (Elderly/Adult)
Omeprazole	20mg bid	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	385.87(348.00–424.00) 10.04(9.20–10.88)	380.94(350.00–412.00) 10.53(9.69–11.38)	0.99 1.05
Ilaprazole	10mg qd	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	208.60(197.80–219.50) 6228.20(5728.20–6728.10)	194.52(181.30–207.70) 5612.20(5026.90–6197.40)	0.93 0.90
Lansoprazole	30mg qd	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	226.38(207.00–245.00) 6937.40(6367.00–7508.00)	236.04(209.00–263.00) 6541.50(5933.00–7150.00)	1.04 0.94
Tramadol	100mg bid	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	393.07(358.00–428.00) 38.88(34.41–43.35)	433.11(382.00–484.00) 44.53(38.14–50.91)	1.10 1.15
Ketoprofen	50mg tid	C_{max} (ug/mL) AUC_{0-t} (ug*h/mL)	3969.60(3694.00–4245.00) 110.41(102.80–118.00)	4354.20(4024.00–4684.00) 117.24(107.60–126.90)	1.10 1.06
Metoprolol	50mg bid	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	451.55(419.00–484.00) 16.86(15.76–17.96)	452.17(420.00–485.00) 17.29(16.20–18.38)	1.00 1.03
Tacrolimus	5mg bid	C_{max} (ng/mL) AUC_{0-t} (ug*h/mL)	123.82(112.90–134.70) 11.91(10.20–13.60)	119.47(107.00–132.00) 11.87(10.00–13.70)	0.96 1.00
Ciclosporin	300mg qd	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	17.90(16.50–19.40) 2211.90(1949.30–2474.60)	18.81(17.53–20.88) 2309.8(2102.00–2517.50)	1.05 1.04
Ondansetron	8mg tid	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	76.01(68.84–83.19) 4594.60(4149.20–5040.00)	82.76(74.03–91.48) 4877.60(4321.70–5433.60)	1.09 1.06
Varenicline	1mg bid	C_{max} (ng/mL) AUC_{0-t} (ng*h/mL)	13.90(12.30–15.40) 1695.30(1617.00–1773.50)	14.10(13.30–14.80) 1987.00(1882.60–2091.40)	1.01 1.17

Abbreviations: qd, once daily; bid, twice daily; tid, three times a day;

consistently remains within the therapeutic reference range. It was worth noting that the laboratory alert concentration for sertraline was set at 300 ng/mL. Remarkably, the steady-state peak concentration remained well below this cautionary threshold, even when administering the maximum daily dosage of 200 mg. Hence, according to the simulation results, it was deduced that elderly individuals might adhere to the recommended dosing regimen as outlined in the package insert, which prescribed a daily administration of 50 mg. In cases of suboptimal clinical efficacy, an escalation of the maximum dosage to 200 mg per day was permissible. Within this defined dosage range, the C_{ss} of sertraline in elderly patients consistently remained within the therapeutic reference range, thus ensuring the treatment effectiveness and reducing potential safety-related concerns.

Recommendation for Alprazolam

In the case of alprazolam, after administration of 0.2 mg three times a day for 7 days (regimen a), the C_{ss} in virtual elderly subjects did not achieve the therapeutic reference range (Figure 4B-a). When the dosage was increased to 0.4 mg three times a day (regimen b) starting on the third day (Figure 4B-b), the mean concentration largely fell within the therapeutic reference range. However, the lower limit of the 90% confidence interval for trough concentration remained below the therapeutic reference range. Following the transition to regimen c, where the dosage was increased to 0.6 mg three times a day starting from the fifth day (as indicated in Figure 4B-c), the mean concentration completely fell within the therapeutic reference range. Furthermore, when the dosage was further elevated from 0.6 mg to 0.8 mg three times a day on day 7 (as shown in Figure 4B-d), the mean concentration was still well within the therapeutic reference range. Even with the total daily dose escalated to 2.4 mg (0.8 mg three times a day), twice the common clinical dose of 1.2 mg (0.4 mg three times a day), the steady-state peak concentration of alprazolam remained below 20 ng/mL. This concentration was significantly lower than the laboratory alert concentration for alprazolam, which was 100 ng/mL.

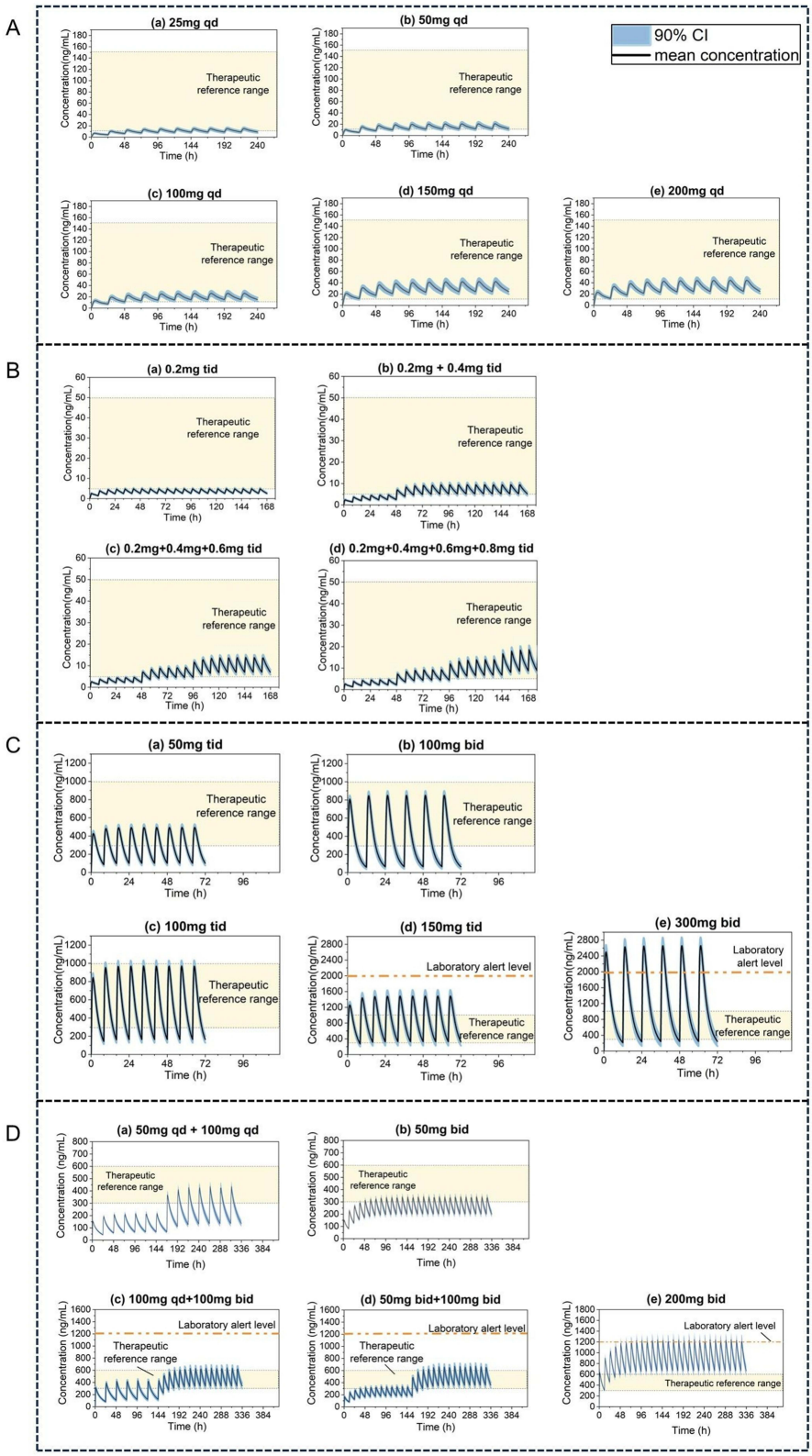

Figure 4 Prediction of pharmacokinetics of four drugs in Chinese elderly population. (**A**) sertraline; (**B**) alprazolam; (**C**) moclobemide; (**D**) amantadine; the black curve represents the predicted mean blood concentration curve, the shaded blue part represents the 90% confidence interval for blood concentration, the shaded yellow part represents the therapeutic reference concentration range, and the dashed Orange line represents the laboratory alert concentration.

Therefore, when prescribed for elderly patients, it was concluded that alprazolam should be administered following the dosage instructions specified in the product package insert.

Recommendation for Moclobemide

The study evaluated five dose regimens for moclobemide using model simulations. None of these regimens resulted in C_{ss} being entirely within the therapeutic reference range (Figure 4C-a~e). Specifically, the 100 mg twice a day (Figure 4C-b) and the 100 mg three times a day (Figure 4C-c) maintained C_{ss} mostly within the therapeutic reference range. However, the 150 mg three times a day (Figure 4C-d) resulted in peak concentrations approaching the laboratory cautionary level (2000 ng/mL). When the daily dose was increased to 600 mg (Figure 4C-e), the C_{ss} exceeded the acceptable limit. In summary, the dosage of moclobemide for elderly patients should be reduced appropriately. It was recommended to administer either 100 mg twice or three times daily, ensuring that the C_{ss} remained within the therapeutic reference range for most of the dosing interval.

Recommendation for Amantadine

For amantadine, the simulation results (Figure 4D-a~e) indicated that two specific dose regimens consistently maintained C_{ss} within the therapeutic reference range. These regimens involved either an initial two-week administration of 50 mg twice daily, followed by an increase to 100 mg twice daily (Figure 4D-d), or an initial 100 mg once daily for 2 weeks, followed by a continuous 100 mg twice daily (Figure 4D-c). Hence, these dose regimens were recommended for the elderly patients.

Discussion

Due to the unique characteristics of the elderly population, there is a significant lack of comprehensive pharmacokinetic data for numerous drugs relevant to this group. As a result, evidence-based guidance is notably absent in multiple domains, including medication utilization and TDM for the elderly. In our study, we selected 50 commonly prescribed drugs for elderly patients in China, encompassing 15 distinct disease areas. Using PBPK modeling, we successfully simulated the pharmacokinetic profiles of these drugs within the elderly population of China. This research addressed the pharmacokinetic data gap in elderly patients and evaluated recommended dosing regimens for this demographic. Additionally, it provided robust support for TDM studies related to four neuropharmacological drugs. The results may also highlight the potential application of integrating the PBPK model with therapeutic drug monitoring for personalized medicine.

PBPK Modeling for 50 Representative Drugs in Chinese Elderly

The results indicated that among the PBPK models for 50 different drugs, there were relatively good matches between clinical observations and simulated drug–time curves in both the absorption and elimination phases. In the comparison of simulated and observed PK parameters, the ratios of C_{max} fell within the range of 0.76 to 1.44, and the ratios of AUC ranged from 0.61 to 1.41, suggesting the models in Chinese young and middle-aged population were well validated. Each model demonstrated a good predictive capability for the PK characteristics of drugs in the elderly population.

Due to the limited number of clinical trials conducted in the elderly population in China, this study lacked clinically observed data for the elderly cohort. The PEAR physiology database in Gastroplus is constructed based on an extensive foundation of literature and statistics, and it has undergone validation through multiple published studies. For example, the PBPK model for the hydrobromide salt of danirixin in the elderly population was established using Gastroplus.[156]

Furthermore, we retrieved major organ weights of Chinese elderly individuals from the literature, which involved the statistical analysis of tens of thousands of autopsy cases in China.[157,158] The physiological parameters of the elderly population generated by PEAR with those provided in the literature are compared in Supplementary Table 3. The results showed that there were no significant differences. Therefore, considering the maturity of the physiological database in Gastroplus, the PBPK models established for the elderly population in this study demonstrated reliable predictive capabilities.

Comparing Pharmacokinetics Between Elderly and Young or Middle-Aged Populations in China

In this study, PBPK models were utilized to predict the PK characteristics of 50 drugs under the same dosing regimen in both the elderly and young and middle-aged populations in China. A comparison was then conducted. Among these 50 drugs, the ratios of PK parameters between the elderly and young and middle-aged populations ranged from 0.81 to 1.29, all of which were close to 1. Thus, the PK features of the two populations exhibited negligible differences. However, this did not conclusively determine whether dose adjustments or optimizations were ultimately needed for the 50 drugs. For example, midazolam. Previous studies demonstrated that the pharmacokinetics of midazolam were unaffected by age.[159–161] Nevertheless, the label for midazolam still recommended the lower doses for elderly individuals.[162]

Therefore, when adjusting the dosage, a thorough evaluation of the patient's physiological condition is necessary. For certain sensitive drugs, monitoring drug concentrations or responses of patients is essential to ensure the safe and effective medication use. The PK characteristics predicted and described by the PBPK models offer the most direct data support for dose adjustments and personalized drug administration.

Application to Support Clinical Rational Dosage for Neuropsychiatric Drugs

The individual differences in the pharmacokinetics of neuropsychiatric drugs are considerable, and elderly individuals exhibit heightened sensitivity to their adverse reactions. Therefore, TDM can effectively enhance the rational use of neuropsychiatric drugs.[163] Using the PBPK models enabled the accurate prediction of plasma drug concentrations in the elderly. By assessing whether C_{ss} falls within the therapeutic reference range, it assisted in providing rational drug dosing regimens in TDM, thereby reducing the risks and costs caused by the approach of trial-and-error.

For sertraline, the drug label recommends a daily dosage of 50 mg. Patients with poor therapeutic response but good tolerability can increase the dosage, with a maximum daily dose of 200 mg for sertraline. Results from the PBPK model simulating dosing regimens in the elderly population indicated that there was little difference in PK parameters between elderly and young and middle-aged adults. Elderly individuals could follow the recommended dosage of 50 mg/day as per the label, and if the therapeutic response was inadequate, the dose could be escalated to 200 mg/day based on individual patient response while maintaining plasma concentrations within the therapeutic reference range.

For alprazolam, the drug label recommends initiating therapy in adults with a dose of 0.4 mg three times a day (tid). However, due to increased sensitivity in the elderly population, it is advised to start with a lower dose of 0.2 mg tid. The simulated results from the PBPK model revealed that, under the same dosing regimen, the value of AUC for elderly population was 1.2 times that of young and middle-aged adults, representing a 20% increase in the value of AUC for the elderly. This difference likely attributed to a decline in metabolic capacity in the elderly, leading to a reduction in the clearance of alprazolam. This also indicated that caution should be exercised when selecting the initial dosage for the elderly. The simulated results indicated that at a dosage of 0.2 mg tid, the virtual patient's drug concentration did not reach the effective therapeutic level. However, upon escalation to 0.6 mg tid and 0.8 mg tid, C_{ss} reached the effective therapeutic range and was significantly lower than the laboratory alert concentration. Therefore, it is advisable to recommend a relatively rapid escalation for elderly patients from 0.2 mg to 0.8 mg tid to achieve therapeutic effects promptly. Subsequent dose adjustments could then be considered based on the individual patient's response.

The PK characteristics of moclobemide in elderly population were simulated, indicating that there was no significant difference in PK parameters between the elderly and the young and middle-aged populations. The value of C_{max} in the elderly population was nearly identical to that in the young and middle-aged population, but the AUC was slightly higher in the elderly, by 14%, compared to the young and middle-aged population. Since moclobemide is metabolized primarily by the liver, age-induced decline in renal clearance contributed less to changes in the PK characteristics. The recommended therapeutic dosage in the label for moclobemide in the antidepressant indication is 300–450 mg/day, with a maximum dose of 600 mg/day. The dosage should be appropriately reduced for elderly patients. We predicted the drug concentrations in elderly individuals under various dosing regimens. The C_{ss} for most of the time after dosing with 100 mg bid (200 mg/day) and 100 mg tid (300 mg/day) were within the therapeutic reference range. However, unlike the information provided in the drug label, dosing with 150 mg tid (450 mg/day) resulted in drug concentrations exceeding

the therapeutic reference range frequently. If there is a need to increase the dosage to this level, close attention should be paid to the response in elderly individuals. After the administration of 300 mg bid (600 mg/day), the peak concentration exceeded the laboratory alert concentration (2000 ng/mL). Consequently, it is not recommended to increase the dose to this dosing regimen in the elderly population.

Amantadine has a high bioavailability and is primarily eliminated through the kidney. Due to the decrease in kidney clearance in the elderly, both C_{max} and AUC in the elderly increased by 11% and 16%, respectively. The recommended dose of amantadine for adults in the instructions is 100 mg qd or bid, and the maximum daily dose is 400 mg. For the elderly population, the instructions do not give a specific dose regimen, only points out that the elderly should use with caution. The PBPK model predicted that an increase of 50 mg bid to 100 mg bid after two weeks or an increase of 100 mg qd dose to 100 mg bid after two weeks would eventually achieve a C_{ss} that could be maintained within the therapeutic reference range. For 200mg bid (400mg/day), the lowest drug concentration exceeded the therapeutic reference range, and the highest concentration reached laboratory alert levels. Therefore, it is recommended for the elderly to be administered at a 100mg bid dose, and higher doses are not recommended unless the patient exhibits good tolerance and the therapeutic effects are not evident.

In summary, rational drug use is very important for the elderly population. However, due to the lack of pharmacokinetic data in the elderly population, the realization of rational drug use is difficult. In the present study, we constructed PBPK models for 50 commonly used drugs of the elderly, aiming to explore the application of PBPK modeling in rational drug use and to optimize the drug administration scheme for the elderly with new technology, as well as to meet the needs of individualized drug use needs in the elderly population.

Although the PBPK models we constructed have stable structures and accurate predictions, they may have some limitations. Due to the lack of data, external validations of the models were not performed using clinical observational data from the elderly population, and pharmacodynamic characteristics were not considered in predicting dosing regimens. No explicit analysis was conducted by categorizing the 50 drugs based on their mechanisms of action to obtain more precise predictive results. Moreover, a factor that the relationship between exposure and safety in the elderly may differ from that in adults was not taken into account in this study. Additionally, hypothesis testing was not performed due to study design constraints, which limits the formal validation of our model predictions. The impact of genetic polymorphism, concurrent medication use, disease influence, and drug metabolites was also not fully considered. Further studies will be conducted to elucidate these issues by incorporating more real-world elderly data and performing sensitivity analyses.

Conclusion

In conclusion, we have developed PBPK models for 50 commonly prescribed drugs within the Chinese elderly population. Subsequently, we tackled prevailing data gaps associated with these specific medications. This study offered an alternative approach for therapeutic drug monitoring, thereby providing crucial data support to enhance the rational administration of medications among the elderly population in China.

Abbreviations

PK, pharmacokinetic; PBPK, Physiologically Based Pharmacokinetic model; ADME, absorption, distribution, metabolism, and excretion; TDM, therapeutic drug monitoring; PMI, potentially inappropriate medication; NCA, Noncompartmental analysis; PEAR, Population Estimates for Age-Related Physiology; BMI, Body Mass Index; GFR, glomerular filtration rate; ACAT, Advanced compartmental absorption and transit; CL, clearance; CYP450, cytochrome 450; tid, three times a day; Css, steady-state plasma concentration.

Acknowledgments

We thank all the contributors for their invaluable contributions to this article.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This research was supported by the National High Level Hospital Clinical Research Funding (2022-PUMCH-B-118) and Capital's Funds for Health Improvement and Research (grant number 2022-2Z-4018).

Disclosure

The authors report no conflicts of interest in this work.

References

1. Marsousi N, Desmeules JA, Rudaz S, Daali Y. Usefulness of PBPK modeling in incorporation of clinical conditions in personalized medicine. *J Pharm Sci*. 2017;106(9):2380–2391. doi:10.1016/j.xphs.2017.04.035
2. Shi S, Klotz U. Age-related changes in pharmacokinetics. *Curr Drug Metab*. 2011;12(7):601–610. doi:10.2174/138920011796504527
3. Statistics NBo. Bulletin of the seventh National Census. Available from: http://www.stats.gov.cn/xxgk/sjfb/zxfb2020/202105/t20210511_1817200.html. Accessed May 1, 2022.
4. Wang J, Li ZX, Qiu CX, Wang D, Cui QH. The relationship between rational drug design and drug side effects. *Brief Bioinform*. 2012;13(3):377–382. doi:10.1093/bib/bbr061
5. Shen C, Shao W, Wang W, et al. Physiologically based pharmacokinetic modeling of levetiracetam to predict the exposure in hepatic and renal impairment and elderly populations. *CPT Pharmacometrics Syst Pharmacol*. 2023;12(7):1001–1015. doi:10.1002/psp4.12971
6. Turnheim K. Drug dosage in the elderly. Is it rational? *Drugs Aging*. 1998;13(5):357–379. doi:10.2165/00002512-199813050-00003
7. Lin W, Chen Y, Unadkat JD, Zhang X, Wu D, Heimbach T. Applications, challenges, and outlook for PBPK modeling and simulation: a regulatory, industrial and academic perspective. *Pharm Res*. 2022;39(8):1701–1731. doi:10.1007/s11095-022-03274-2
8. Sager JE, Yu J, Ragueneau-Majlessi I, Isoherranen N. Physiologically based pharmacokinetic (PBPK) modeling and simulation approaches: a systematic review of published models, applications, and model verification. *Drug Metab Dispos*. 2015;43(11):1823–1837. doi:10.1124/dmd.115.065920
9. Samuel MJ. American geriatrics society 2023 updated AGS beers criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2023;71(7):2052–2081. doi:10.1111/jgs.18372
10. Zhang Y, Chen Z, Tian F. Potentially inappropriate medications in older Chinese outpatients based on the beers criteria and Chinese criteria. *Front Pharmacol*. 2022;13:991087. doi:10.3389/fphar.2022.991087
11. Bi YA, Lin J, Mathialagan S, et al. Role of hepatic organic anion transporter 2 in the pharmacokinetics of R- and S-warfarin: in vitro studies and mechanistic evaluation. *Mol Pharm*. 2018;15(3):1284–1295. doi:10.1021/acs.molpharmaceut.7b01108
12. Yan H. *Pharmacokinetics/Pharmacokinetics of 2.5mg/5mg warfarin sodium tablets in healthy Chinese*. master. Peking Union Medical College, Chinese Academy of Medical Sciences, Tsinghua University, Chinese Union Medical College; 2004. Avaialble from: https://d-wanfangdata-com-cn-443.webvpn.cams.cn/thesis/ChJUaGVzaXNOZXdTMjAyMzAxMTISB1k2ODEyNjEaCDlzN253N2hl. Accessed April 8, 2025.
13. Gao H, Yao L, Mathieu HW, et al. In silico modeling of nonspecific binding to human liver microsomes. *Drug Metab Dispos*. 2008;36(10):2130–2135. doi:10.1124/dmd.107.020131
14. Kazui M, Nishiya Y, Ishizuka T, et al. Identification of the human cytochrome P450 enzymes involved in the two oxidative steps in the bioactivation of clopidogrel to its pharmacologically active metabolite. *Drug Metab Dispos*. 2010;38(1):92–99. doi:10.1124/dmd.109.029132
15. Rodgers T, Leahy D, Rowland M. Physiologically based pharmacokinetic modeling 1: predicting the tissue distribution of moderate-to-strong bases. *J Pharm Sci*. 2005;94(6):1259–1276. doi:10.1002/jps.20322
16. Rodgers T, Leahy D, Rowland M. Tissue distribution of basic drugs: accounting for enantiomeric, compound and regional differences amongst beta-blocking drugs in rat. *J Pharm Sci*. 2005;94(6):1237–1248. doi:10.1002/jps.20323
17. Rodgers T, Rowland M. Physiologically based pharmacokinetic modelling 2: predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. *J Pharm Sci*. 2006;95(6):1238–1257. doi:10.1002/jps.20502
18. Rodgers T, Rowland M. Mechanistic approaches to volume of distribution predictions: understanding the processes. *Pharm Res*. 2007;24(5):918–933. doi:10.1007/s11095-006-9210-3
19. Uchimura T, Kato M, Saito T, Kinoshita H. Prediction of human blood-to-plasma drug concentration ratio. *Biopharm Drug Dispos*. 2010;31(5–6):286–297. doi:10.1002/bdd.711
20. Zeeh J, Platt D. The aging liver: structural and functional changes and their consequences for drug treatment in old age. *Gerontology*. 2002;48(3):121–127. doi:10.1159/000052829
21. Teng R, Oliver S, Hayes MA, Butler K. Absorption, distribution, metabolism, and excretion of ticagrelor in healthy subjects. *Drug Metab Dispos*. 2010;38(9):1514–1521. doi:10.1124/dmd.110.032250
22. Zhang M, You X, Ke M, et al. Prediction of ticagrelor and its active metabolite in liver cirrhosis populations using a physiologically based pharmacokinetic model involving pharmacodynamics. *J Pharm Sci*. 2019;108(8):2781–2790. doi:10.1016/j.xphs.2019.03.028
23. Zhou D, Andersson TB, Grimm SW. In vitro evaluation of potential drug-drug interactions with ticagrelor: cytochrome P450 reaction phenotyping, inhibition, induction, and differential kinetics. *Drug Metab Dispos*. 2011;39(4):703–710. doi:10.1124/dmd.110.037143

24. Li H, Butler K, Yang L, Yang Z, Teng R. Pharmacokinetics and tolerability of single and multiple doses of ticagrelor in healthy Chinese subjects: an open-label, sequential, two-cohort, single-centre study. *Clin Drug Investig*. 2012;32(2):87–97. doi:10.2165/11595930-000000000-00000
25. Teng R, Mitchell P, Butler K. Effect of age and gender on pharmacokinetics and pharmacodynamics of a single ticagrelor dose in healthy individuals. *Eur J Clin Pharmacol*. 2012;68(8):1175–1182. doi:10.1007/s00228-012-1227-4
26. Grillo JA, Zhao P, Bullock J, et al. Utility of a physiologically-based pharmacokinetic (PBPK) modeling approach to quantitatively predict a complex drug-drug-disease interaction scenario for rivaroxaban during the drug review process: implications for clinical practice. *Biopharm Drug Dispos*. 2012;33(2):99–110. doi:10.1002/bdd.1771
27. Mueck W, Kubitza D, Becka M. Co-administration of rivaroxaban with drugs that share its elimination pathways: pharmacokinetic effects in healthy subjects. *Br J Clin Pharmacol*. 2013;76(3):455–466. doi:10.1111/bcp.12075
28. Huawei W, Ming Y, Xiaobin L, et al. Bioequivalence study of rivaroxaban tablets in Chinese healthy volunteers. *Chin J Clin Pharmacol*. 2020;36(22):3590–3594. doi:10.13699/j.cnki.1001-6821.2020.22.005
29. Jiang J, Hu Y, Zhang J, et al. Safety, pharmacokinetics and pharmacodynamics of single doses of rivaroxaban - an oral, direct factor Xa inhibitor - in elderly Chinese subjects. *Thromb Haemost*. 2010;103(1):234–241. doi:10.1160/th09-03-0196
30. Damle B, Varma MV, Wood N. Pharmacokinetics of voriconazole administered concomitantly with fluconazole and population-based simulation for sequential use. *Antimicrob Agents Chemother*. 2011;55(11):5172–5177. doi:10.1128/aac.00423-11
31. Dong J, Liu SB, Rasheduzzaman JM, Huang CR, Miao LY. Development of physiology based pharmacokinetic model to predict the drug interactions of voriconazole and venetoclax. *Pharm Res*. 2022;39(8):1921–1933. doi:10.1007/s11095-022-03289-9
32. Wang G, Lei HP, Li Z, et al. The CYP2C19 ultra-rapid metabolizer genotype influences the pharmacokinetics of voriconazole in healthy male volunteers. *Eur J Clin Pharmacol*. 2009;65(3):281–285. doi:10.1007/s00228-008-0574-7
33. Arredondo G, Calvo R, Marcos F, Martínez-Jordá R, Suarez E. Protein binding of itraconazole and fluconazole in patients with cancer. *Int J Clin Pharmacol Ther*. 1995;33(8):449–452.
34. watt KM, Cohen-Wolkowiez M, Barrett JS, et al. Physiologically based pharmacokinetic approach to determine dosing on extracorporeal life support: fluconazole in children on ECMO. *CPT Pharmacometrics Syst Pharmacol*. 2018;7(10):629–637. doi:10.1002/psp4.12338
35. Guo T, Sun WJ, Xia DY, Zhao LS. The pharmacokinetics of fluconazole in healthy Chinese adult volunteers: influence of ethnicity and gender. *J Clin Pharm Ther*. 2010;35(2):231–237. doi:10.1111/j.1365-2710.2009.01097.x
36. Moj D, Hanke N, Britz H, et al. Clarithromycin, midazolam, and digoxin: application of PBPK modeling to gain new insights into drug-drug interactions and co-medication regimens. *Aaps J*. 2017;19(1):298–312. doi:10.1208/s12248-016-0009-9
37. Rodrigues AD, Roberts EM, Mulford DJ, Yao Y, Ouellet D. Oxidative metabolism of clarithromycin in the presence of human liver microsomes. Major role for the cytochrome P4503A (CYP3A) subfamily. *Drug Metab Dispos*. 1997;25(5):623–630.
38. Yuanwei J, Jie S, Haitang X, et al. Bioequivalence study of clarithromycin tablets in healthy Chinese subjects. *Chin J Clin Pharmacol*. 2020;36(21):3504–3508. doi:10.13699/j.cnki.1001-6821.2020.21.027
39. Lixin Y, Jinmin R, Chuanping W, Qian S, Shumei W. Pharmacokinetics and bioequivalence of clarithromycin tablets in healthy subjects. *Chin Pharmaceut Industry*. 2008;2008(21):12–14.
40. Ferreira A, Martins H, Oliveira JC, Lapa R, Vale N. PBPK modeling and simulation of antibiotics amikacin, gentamicin, tobramycin, and vancomycin used in hospital practice. *Life*. 2021;11(11). doi:10.3390/life11111130
41. Radke C, Horn D, Lanckohr C, et al. Development of a physiologically based pharmacokinetic modelling approach to predict the pharmacokinetics of vancomycin in critically ill septic patients. *Clin Pharmacokinet*. 2017;56(7):759–779. doi:10.1007/s40262-016-0475-3
42. Zhou W, Johnson TN, Xu H, et al. Predictive performance of physiologically based pharmacokinetic and population pharmacokinetic modeling of renally cleared drugs in children. *CPT Pharmacometrics Syst Pharmacol*. 2016;5(9):475–483. doi:10.1002/psp4.12101
43. Xiaoduo CXJ. Pharmacokinetics of vancomycin in elderly patients with MRSA lower respiratory tract infection. *Modern Hospital*. 2009;9(08):9–11.
44. Song L, Yu Z, Xu Y, et al. Preliminary physiologically based pharmacokinetic modeling of renally cleared drugs in Chinese pregnant women. *Biopharm Drug Dispos*. 2020;41(6):248–267. doi:10.1002/bdd.2243
45. Guoying C, Chunhua S, Jiying W, Yiming H. Study on the pharmacokinetics of Tannin in healthy people and patients with hemodialysis uremia. *Chin J New Drugs*. 1994;1994(01):48–50+47.
46. Guoying C, Chunhua S, Wongying, Hossen J. Study on pharmacokinetics of tenine in healthy subjects. *Chin J New Drugs*. 1992;1992(06):51–53+50.
47. Clinical pharmacology and biopharmaceutics review for NDA 021130. FDA; 2000. Available from: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2000/21130_Zyvox_biopharmr.pdf. Accessed April 9, 2025.
48. Chakraborty S, Yadav L, Aggarwal D. Prediction of in vivo drug performance using in vitro dissolution coupled with STELLA: a study with selected drug products. *Drug Dev Ind Pharm*. 2015;41(10):1667–1673. doi:10.3109/03639045.2014.991399
49. Gandelman K, Zhu T, Fahmi OA, et al. Unexpected effect of rifampin on the pharmacokinetics of linezolid: in silico and in vitro approaches to explain its mechanism. *J Clin Pharmacol*. 2011;51(2):229–236. doi:10.1177/0091270010366445
50. Guofang H, Qiao S, Ding Y, et al. Fasting and postprandial pharmacokinetics of linezolid in healthy Chinese subjects [J]. *Chin J Clin Pharmacol*. 2015;31(23):2314–2316. doi:10.13699/j.cnki.1001-6821.2015.23.012
51. Pollock BG. Citalopram: a comprehensive review. *Expert Opin Pharmacother*. 2001;2(4):681–698. doi:10.1517/14656566.2.4.681
52. von Moltke LL, Greenblatt DJ, Grassi JM, et al. Citalopram and desmethylcitalopram in vitro: human cytochromes mediating transformation, and cytochrome inhibitory effects. *Biol Psychiatry*. 1999;46(6):839–849. doi:10.1016/s0006-3223(98)00353-9
53. Lei L. *Determination of Plasma Concentration of Citalopram by HPLC and Its Pharmacokinetics and Relative Bioavailability. Master*. hebei: medical university; 2005.
54. Lijuan Z, Fang T. Effect of CYP2C19 genetic polymorphism on citalopram metabolism in healthy Chinese subjects. *Chin J Clin Pharmacol*. 2014;30(04):324–326+331. doi:10.13699/j.cnki.1001-6821.2014.04.022
55. Jin M, Peiqin M, Chunxiang Z, Xiaoli S. Human pharmacokinetics of venlafaxine. *Chin J PLA Pharm*. 2008;24(06):504–507.
56. Sutton SC. Role of physiological intestinal water in oral absorption. *Aaps J*. 2009;11(2):277–285. doi:10.1208/s12248-009-9087-2

57. Templeton IE, Chen Y, Mao J, et al. Quantitative prediction of drug-drug interactions involving inhibitory metabolites in drug development: how can physiologically based pharmacokinetic modeling help? *CPT Pharmacometrics Syst Pharmacol*. 2016;5(10):505–515. doi:10.1002/psp4.12110
58. Yuqing X, Changchang Y, Huijie Z, Wenwei X. Pharmacokinetics of sertraline in Chinese healthy volunteers. *Chin Pharmacol Bull*. 2006;(05):616–619.
59. Zhang M, Gao F, Cui X, Zhang Y, Sun Y, Gu J. Development and validation of an improved method for the quantitation of sertraline in human plasma using LC-MS-MS and its application to bioequivalence studies. *J Chromatogr Sci*. 2011;49(2):89–93. doi:10.1093/chrsci/49.2.89
60. Rasool MF, Läer S. Development and evaluation of a physiologically based pharmacokinetic model to predict carvedilol-paroxetine metabolic drug-drug interaction in healthy adults and its extrapolation to virtual chronic heart failure patients for dose optimization. *Expert Opin Drug Metab Toxicol*. 2021;17(6):717–724. doi:10.1080/17425255.2021.1921145
61. Jun Z, Weizhong L, Hong Y, et al. Pharmacokinetics of Paxil tablets in healthy subjects. *J Southern Med Univ*. 2008;28(2):260–262.
62. Tylutki Z, Mendyk A, Polak S. Mechanistic physiologically based pharmacokinetic (PBPK) model of the heart accounting for inter-individual variability: development and performance verification. *J Pharm Sci*. 2018;107(4):1167–1177. doi:10.1016/j.xphs.2017.11.012
63. Ping LJ-l L, Yucun S, liang S, Lili S, Yuwen H, Ailin Z. Pharmacokinetics of amitriptyline and its major metabolites in healthy young adults. *Chin J Clin Pharmacol*. 1992;(01):1–6. doi:10.13699/j.cnki.1001-6821.1992.01.001
64. Zhai Y, Wu L, Zheng Y, et al. Bioequivalence study of amitriptyline hydrochloride tablets in healthy Chinese volunteers under fasting and fed conditions. *Drug Des Devel Ther*. 2020;14:3131–3142. doi:10.2147/dddt.S258173
65. Virtanen R, Scheinin M, Iisalo E. Single dose pharmacokinetics of doxepin in healthy volunteers. *Acta Pharmacol Toxicol*. 1980;47(5):371–376. doi:10.1111/j.1600-0773.1980.tb01575.x
66. Nguyen HQ, Callegari E, Obach RS. The use of in vitro data and physiologically-based pharmacokinetic modeling to predict drug metabolite exposure: desipramine exposure in cytochrome P4502D6 extensive and poor metabolizers following administration of imipramine. *Drug Metab Dispos*. 2016;44(10):1569–1578. doi:10.1124/dmd.116.071639
67. Samant TS, Lukacova V, Schmidt S. Development and qualification of physiologically based pharmacokinetic models for drugs with atypical distribution behavior: a desipramine case study. *CPT Pharmacometrics Syst Pharmacol*. 2017;6(5):315–321. doi:10.1002/psp4.12180
68. Rudorfer MV, Lane EA, Chang WH, Zhang MD, Potter WZ. Desipramine pharmacokinetics in Chinese and Caucasian volunteers. *Br J Clin Pharmacol*. 1984;17(4):433–440. doi:10.1111/j.1365-2125.1984.tb02368.x
69. Iga K. Use of three-compartment physiologically based pharmacokinetic modeling to predict hepatic blood levels of fluvoxamine relevant for drug-drug interactions. *J Pharm Sci*. 2015;104(4):1478–1491. doi:10.1002/jps.24320
70. Kanacher T, Lindauer A, Mezzalana E, et al. 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. *Pharmaceutics*. 2020;12(12):1191. doi:10.3390/pharmaceutics12121191
71. Ruomei X, Chunxia W, Lianbing H. Study on human bioequivalence of domestic and imported fluvoxamine maleate tablets. *Chin Pharm*. 2010;21(26):2444–2446.
72. Ming Z, Guocheng L, Guicheng Z, et al. Determination of fluvoxamine concentration in human plasma and its bioequivalence by LC-MS/MS. *Chin J Clin Pharm*. 2011;20(05):257–261. doi:10.19577/j.cnki.issn10074406.2011.05.001
73. Jingping Z, Xiaogang C, Yuanguang C, Jindong C, Ronghua Z, Zhimin X. Study on relative bioavailability of domestic moclobemide tablets. *Chin J Clin Pharmacol*. 1998;1998(03):39–42.
74. Hongyan Z, Tianmei S, Ping L, Hong M, Liang S. Phase I clinical trial study of domestic Moclobemide. *Chin J Clin Pharmacol*. 1999;(05):352–356. doi:10.13699/j.cnki.1001-6821.1999.05.009
75. Jornil J, Jensen KG, Larsen F, Linnet K. Risk assessment of accidental nortriptyline poisoning: the importance of cytochrome P450 for nortriptyline elimination investigated using a population-based pharmacokinetic simulator. *Eur J Pharm Sci*. 2011;44(3):265–272. doi:10.1016/j.ejps.2011.08.003
76. Liedholm H, Lidén A. Food intake and the presystemic metabolism of single doses of amitriptyline and nortriptyline. *Fundam Clin Pharmacol*. 1998;12(6):636–642. doi:10.1111/j.1472-8206.1998.tb00998.x
77. Jeong HC, Chae YJ, Lee S, Kang W, Yun HY, Shin KH. Prediction of fluoxetine and norfluoxetine pharmacokinetic profiles using physiologically based pharmacokinetic modeling. *J Clin Pharmacol*. 2021;61(11):1505–1513. doi:10.1002/jcph.1927
78. Li C, Ji Z, Nan F, et al. Liquid chromatography/tandem mass spectrometry for the determination of fluoxetine and its main active metabolite norfluoxetine in human plasma with deuterated fluoxetine as internal standard. *Rapid Commun Mass Spectrom*. 2002;16(19):1844–1850. doi:10.1002/rcm.800
79. Li Pengfei MP, Zhuoling AN, Cheng W, Lei Ning YUW, Lihong L. Rapid determination of fluoxetine concentration in human plasma by LC-MS/MS. *Int J Lab Med*. 2015;36(21):3092–3094+3097.
80. Rosenzweig P, Canal M, Patat A, Bergougnan L, Zieleniuk I, Bianchetti G. A review of the pharmacokinetics, tolerability and pharmacodynamics of amisulpride in healthy volunteers. *Hum Psychopharmacol*. 2002;17(1):1–13. doi:10.1002/hup.320
81. Pj B, Sk K, Dubey B. Oral bioavailability enhancement of amisulpride: complexation and its pharmacokinetics and pharmacodynamics evaluations. *Drug Metab Lett*. 2019;13(2):132–144. doi:10.2174/1872312813666191018152226
82. Xian L, Guiyan Y, Benjie W, Ruichen G. Pharmacokinetics and bioequivalence of domestic and imported amisulpride tablets in healthy subjects. *Chin J Clin Pharmacol*. 2010;26(01):33–36. doi:10.13699/j.cnki.1001-6821.2010.01.014
83. Vieira MD, Kim MJ, Apparaju S, et al. PBPK model describes the effects of comedication and genetic polymorphism on systemic exposure of drugs that undergo multiple clearance pathways. *Clin Pharmacol Ther*. 2014;95(5):550–557. doi:10.1038/clpt.2014.43
84. Zheng L, Tang S, Tang R, Xu M, Jiang X, Wang L. Dose adjustment of quetiapine and aripiprazole for pregnant women using physiologically based pharmacokinetic modeling and simulation. *Clin Pharmacokinet*. 2021;60(5):623–635. doi:10.1007/s40262-020-00962-3
85. Hongyun W, Kai S, Ji J, Bei H. The concentrations of aripiprazole and its metabolite dehydroaripiprazole in human plasma were determined by LC-MS/MS. *J Pharm Anal*. 2011;31(07):1278–1282. doi:10.16155/j.0254-1793.2011.07.054
86. Ji B, Liu S, Xue Y, et al. Prediction of drug-drug interactions between opioids and overdosed benzodiazepines using physiologically based pharmacokinetic (PBPK) modeling and simulation. *Drugs R D*. 2019;19(3):297–305. doi:10.1007/s40268-019-00282-3

87. Emoto C, Shimizu M, Tanaka T, Yamazaki H. Feasibility of physiologically based pharmacokinetic simulations for assessing pediatric patients after accidental drug ingestion: a case study of a 1.4-year-old girl who ingested alprazolam. *Drug Metab Pharmacokinet*. 2021;39:100394. doi:10.1016/j.dmpk.2021.100394
88. Hui G, Lei S, Shujin Z, Xiaohui Z, Yan L. Pharmacokinetics of alprazolam in Han Chinese patients with CYP3A5*3/*3 genotype generalized anxiety disorder. 2012;101–106.
89. Kaplan GB, Greenblatt DJ, Ehrenberg BL, Goddard JE, Harmatz JS, Shader RI. Single-dose pharmacokinetics and pharmacodynamics of alprazolam in elderly and young subjects. *J Clin Pharmacol*. 1998;38(1):14–21. doi:10.1002/j.1552-4604.1998.tb04370.x
90. Kneller LA, Abad-Santos F, Hempel G. Physiologically based pharmacokinetic modelling to describe the pharmacokinetics of risperidone and 9-hydroxyrisperidone according to cytochrome P450 2D6 phenotypes. *Clin Pharmacokinet*. 2020;59(1):51–65. doi:10.1007/s40262-019-00793-x
91. Xia Z, Jingli D, Xiao L, et al. Bioequivalence of imported and domestic risperidone film coated tablets in healthy volunteers. *Chin J Clin Pharmacol*. 2009;25(04):312–315. doi:10.13699/j.cnki.1001-6821.2009.04.022
92. Liu Y, Zhang MQ, Jia JY, et al. Bioequivalence and pharmacokinetic evaluation of two formulations of risperidone 2 mg: an open-label, single-dose, fasting, randomized-sequence, two-way crossover study in healthy male Chinese volunteers. *Drugs R D*. 2013;13(1):29–36. doi:10.1007/s40268-012-0002-4
93. Khalid S, Rasool MF, Imran I, et al. A physiologically based pharmacokinetic model for predicting diazepam pharmacokinetics after intravenous, oral, intranasal, and rectal applications. *Pharmaceutics*. 2021;13(9):1480. doi:10.3390/pharmaceutics13091480
94. Wang LL, Ren XX, He Y, et al. Study on the pharmacokinetics of diazepam and its metabolites in blood of Chinese people. *Eur J Drug Metab Pharmacokinet*. 2020;45(4):477–485. doi:10.1007/s13318-020-00614-8
95. Hayden FG, Minocha A, Spyker DA, Hoffman HE. Comparative single-dose pharmacokinetics of amantadine hydrochloride and rimantadine hydrochloride in young and elderly adults. *Antimicrob Agents Chemother*. 1985;28(2):216–221. doi:10.1128/aac.28.2.216
96. Wang P, Liang YZ, Chen BM, et al. Quantitative determination of amantadine in human plasma by liquid chromatography-mass spectrometry and the application in a bioequivalence study. *J Pharm Biomed Anal*. 2007;43(4):1519–1525. doi:10.1016/j.jpba.2006.10.044
97. Bin Y, Panqin M, Jin S, Xin X, Mingrui W. The equilibrium solubility and apparent oil-water partition coefficient of pramexole hydrochloride were determined by HPLC. *Chinese J Pharm*. 2016;14(01):26–32. doi:10.14146/j.cnki.cjp.2016.01.004
98. You X, Wu W, Xu J, et al. Development of a physiologically based pharmacokinetic model for prediction of pramipexole pharmacokinetics in Parkinson's disease patients with renal impairment. *J Clin Pharmacol*. 2020;60(8):999–1010. doi:10.1002/jcph.1593
99. Yunxuan Z, Xiaoyan C, Xiaojin S, Jiahong L, Dafang Z, Mingkang Z. Pharmacokinetic study and safety evaluation of pramipexole tablets in healthy Chinese subjects. *Fudan J*. 2015;42(02):235–238.
100. Sinha J, Karatza E, Gonzalez D. Physiologically-based pharmacokinetic modeling of oxcarbazepine and levetiracetam during adjunctive antiepileptic therapy in children and adolescents. *CPT Pharmacometrics Syst Pharmacol*. 2022;11(2):225–239. doi:10.1002/psp4.12750
101. Wenxing L, Yi D, Yanyan J, et al. Pharmacokinetics of levetiracetam tablets in healthy human bodies. *Chin J Clin Pharmacol*. 2012;28 (04):272–274+252. doi:10.13699/j.cnki.1001-6821.2012.04.015
102. Shijia L, Du C, Jungang Y, et al. Pharmacokinetics of levetiracetam injection and levetiracetam tablets in healthy subjects. *Chin J Clin Pharmacol*. 2017;22(03):294–298.
103. Conner TM, Reed RC, Zhang T. A physiologically based pharmacokinetic model for optimally profiling lamotrigine disposition and drug-drug interactions. *Eur J Drug Metab Pharmacokinet*. 2019;44(3):389–408. doi:10.1007/s13318-018-0532-4
104. Dongsheng O, Xiaoping C, Songlin H, et al. Lamotrigine tablets: pharmacokinetics in the human body and relative bioavailability. *Chin J Clin Pharmacol*. 2003;(04):273–276. doi:10.13699/j.cnki.1001-6821.2003.04.008
105. Dickschen K, Willmann S, Thelen K, Lippert J, Hempel G, Eissing T. Physiologically based pharmacokinetic modeling of tamoxifen and its metabolites in women of different CYP2D6 phenotypes provides new insight into the tamoxifen mass balance. *Front Pharmacol*. 2012;3:92. doi:10.3389/fphar.2012.00092
106. Xie Lin LX, Xiao Jian G, Guoqing L. Pharmacokinetics and relative bioavailability of Tamoxifen citrate tablets. *J China Pharmaceut Univ*. 1995;1995(02):84–86.
107. Adiwidjaja J, Boddy AV, McLachlan AJ. Physiologically-based pharmacokinetic predictions of the effect of curcumin on metabolism of imatinib and bosutinib. *Vitro and in Vivo Disconnect Pharm Res*. 2020;37(7):128. doi:10.1007/s11095-020-02834-8
108. Jing P, Zhicheng G. Determination of imatinib in human plasma by LC-MS/MS method and bioequivalence evaluation. *Chin J Pharmaceut Industry*. 2015;46(09):991–995. doi:10.16522/j.cnki.cjph.2015.09.013
109. Jing L, Wencao Z, Ren X, Jintong L. Bioequivalence study of imatinib mesylate tablets in healthy Chinese male subjects. *Chin J Clin Pharmacol*. 2017;33(07):605–608. doi:10.13699/j.cnki.1001-6821.2017.07.009
110. Ding J, Chen X, Gao Z, et al. Metabolism and pharmacokinetics of novel selective vascular endothelial growth factor receptor-2 inhibitor apatinib in humans. *Drug Metab Dispos*. 2013;41(6):1195–1210. doi:10.1124/dmd.112.050310
111. Liu H, Yu Y, Guo N, Wang X, Han B, Xiang X. Application of physiologically based pharmacokinetic modeling to evaluate the drug-drug and drug-disease interactions of apatinib. *Front Pharmacol*. 2021;12:780937. doi:10.3389/fphar.2021.780937
112. Liu X, Zhang Y, Chen Q, et al. Pharmacokinetic drug interactions of apatinib with rifampin and itraconazole. *J Clin Pharmacol*. 2018;58 (3):347–356. doi:10.1002/jcph.1016
113. Chen Y, Zhou D, Tang W, Zhou W, Al-Huniti N, Masson E. Physiologically Based Pharmacokinetic Modeling To Evaluate The Systemic Exposure Of Gefitinib in CYP2D6 ultrarapid metabolizers and extensive metabolizers. *J Clin Pharmacol*. 2018;58(4):485–493. doi:10.1002/jcph.1036
114. Yaqian L, Jie H, Shuang Y, et al. Study on pharmacokinetics and bioequivalence of gefitinib tablets. *Chin J Clin Pharmacol*. 2020;36 (12):1690–1693. doi:10.13699/j.cnki.1001-6821.2020.12.024
115. Chang M, Bathena S, Christopher LJ, Shen H, Roy A. Prediction of drug-drug interaction potential mediated by transporters between dasatinib and metformin, pravastatin, and rosuvastatin using physiologically based pharmacokinetic modeling. *Cancer Chemother Pharmacol*. 2022;89 (3):383–392. doi:10.1007/s00280-021-04394-z
116. Huaiyou X, Chao S, Feng S, Chunlei T. Determination of dasatinib concentration in human plasma by LC-MS/MS method and study on bioequivalence of two tablets. *Chin Pharm*. 2016;27(08):1051–1054.

117. Zhang T. Physiologically based pharmacokinetic modeling of disposition and drug-drug interactions for atorvastatin and its metabolites. *Eur J Pharm Sci*. 2015;77:216–229. doi:10.1016/j.ejps.2015.06.019
118. Liu YM, Pu HH, Liu GY, et al. Pharmacokinetics and bioequivalence evaluation of two different atorvastatin calcium 10-mg tablets: a single-dose, randomized-sequence, open-label, two-period crossover study in healthy fasted Chinese adult males. *Clin Ther*. 2010;32(7):1396–1407. doi:10.1016/j.clinthera.2010.07.004
119. Hanke N, Gómez-Mantilla JD, Ishiguro N, Stopfer P, Nock V. Physiologically based pharmacokinetic modeling of rosuvastatin to predict transporter-mediated drug-drug interactions. *Pharm Res*. 2021;38(10):1645–1661. doi:10.1007/s11095-021-03109-6
120. Li XN, Xu HR, Chen WL, Chu NN, Zhu JR. Pharmacokinetics of rosuvastatin in healthy Chinese volunteers living in China: a randomized, open-label, ascending single- and multiple-dose study. *Clin Ther*. 2010;32(3):575–587. doi:10.1016/j.clinthera.2010.03.015
121. Yang Y, Li P, Zhang Z, Wang Z, Liu L, Liu X. Prediction of cyclosporin-mediated drug interaction using physiologically based pharmacokinetic model characterizing interplay of drug transporters and enzymes. *Int J Mol Sci*. 2020;21(19):7023. doi:10.3390/ijms21197023
122. Prieto Garcia L, Lundahl A, Ahlström C, Vildhede A, Lennernäs H, Sjögren E. Does the choice of applied physiologically-based pharmacokinetics platform matter? A case study on simvastatin disposition and drug-drug interaction. *CPT Pharmacometrics Syst Pharmacol*. 2022;11(9):1194–1209. doi:10.1002/psp4.12837
123. Zhao Q, Jiang J, Hu P. Effects of four traditional Chinese medicines on the pharmacokinetics of simvastatin. *Xenobiotica*. 2015;45(9):803–810. doi:10.3109/00498254.2015.1019593
124. Xiufeng H, Guanghui L. Pharmacokinetics of fluvastatin sodium alone and nateglinide tablets in vivo. *Chin Prescription Drugs*. 2016;14(09):33–34.
125. Ogilvie BW, Yerino P, Kazmi F, et al. The proton pump inhibitor, omeprazole, but not lansoprazole or pantoprazole, is a metabolism-dependent inhibitor of CYP2C19: implications for coadministration with clopidogrel. *Drug Metab Dispos*. 2011;39(11):2020–2033. doi:10.1124/dmd.111.041293
126. U.S.FOOD & DRUG ADMINISTRATION. Esomeprazole magnesium label. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021153s022lbl.pdf. Accessed April 9, 2025.
127. Zhongliang L, Xiaobo W, Ronggang Y, Wen Y, Xiaonan S. Pharmacokinetic study and bioequivalence evaluation of omeprazole enteric-coated tablets in healthy subjects. *Pharm Care Res*. 2007;2007(06):451–454.
128. Seo KA, Lee SJ, Kim KB, et al. Ilaprazole, a new proton pump inhibitor, is primarily metabolized to ilaprazole sulfone by CYP3A4 and 3A5. *Xenobiotica*. 2012;42(3):278–284. doi:10.3109/00498254.2011.622416
129. Kristl A. Acido-basic properties of proton pump inhibitors in aqueous solutions. *Drug Dev Ind Pharm*. 2009;35(1):114–117. doi:10.1080/03639040802220284
130. Landes BD, Petite JP, Flouvat B. Clinical pharmacokinetics of lansoprazole. *Clin Pharmacokinet*. 1995;28(6):458–470. doi:10.2165/00003088-199528060-00004
131. Zhou W, Johnson TN, Bui KH, et al. Predictive performance of physiologically based pharmacokinetic (PBPK) modeling of drugs extensively metabolized by major cytochrome P450s in children. *Clin Pharmacol Ther*. 2018;104(1):188–200. doi:10.1002/cpt.905
132. Yue Z. *Study on Pharmacokinetics and Bioequivalence of Lansoprazole Tablets in Healthy Subjects*. 硕士. The Fourth Military Medical University; 2011.
133. Long T, Cristofoletti R, Cicali B, et al. Physiologically based pharmacokinetic modeling to assess the impact of CYP2D6-mediated drug-drug interactions on tramadol and O-desmethyltramadol exposures via allosteric and competitive inhibition. *J Clin Pharmacol*. 2022;62(1):76–86. doi:10.1002/jcph.1951
134. T'Jollyn H, Vermeulen A, Van Bocxlaer J. PBPK and its virtual populations: the impact of physiology on pediatric pharmacokinetic predictions of tramadol. *Aaps j*. 2018;21(1):8. doi:10.1208/s12248-018-0277-7
135. Xu M, Zheng L, Zeng J, Xu W, Jiang X, Wang L. Physiologically based pharmacokinetic modeling of tramadol to inform dose adjustment and drug-drug interactions according to CYP2D6 phenotypes. *Pharmacotherapy*. 2021;41(3):277–290. doi:10.1002/phar.2494
136. Lianyong G, Quansheng L, Yibao G, Changxiao L. Pharmacokinetics and bioavailability of ketoprofen sustained-release tablets and regular release tablets in healthy subjects. *Acta Pharma Sin*. 1999;(07):68–72. doi:10.16438/j.0513-4870.1999.07.016
137. Xiaobo W, Zhongliang L, Xiaonan S, et al. Pharmacokinetic study and bioequivalence evaluation of metoprolol tartrate tablets in healthy subjects. *Pharm Care Res*. 2008;2008(04):293–295.
138. Zhang H, Bu F, Li L, et al. Prediction of drug-drug interaction between tacrolimus and principal ingredients of wuzhi capsule in Chinese healthy volunteers using physiologically-based pharmacokinetic modelling. *Basic Clin Pharmacol Toxicol*. 2018;122(3):331–340. doi:10.1111/bcpt.12914
139. Jian L. Study on human pharmacokinetics and bioequivalence of tacrolimus capsules. *Chin J Clin Pharmacol Master*. 2008.
140. Fan J, Chen L, Lu X, Li M, Zhu L. The pharmacokinetic prediction of cyclosporin a after coadministration with wuzhi capsule. *AAPS Pharm Sci Tech*. 2019;20(6):247. doi:10.1208/s12249-019-1444-6
141. Kees F, Bucher M, Schweda F, et al. Comparative bioavailability of the microemulsion formulation of cyclosporine (Neoral) with a generic dispersion formulation (Cicloral) in young healthy male volunteers. *Ther Drug Monit*. 2006;28(3):312–320. doi:10.1097/01.ftd.0000211804.89440.74
142. Zapke SE, Willmann S, Grebe SO, Menke K, Thürmann PA, Schmiedl S. Comparing predictions of a PBPK model for cyclosporine with drug levels from therapeutic drug monitoring. *Front Pharmacol*. 2021;12:630904. doi:10.3389/fphar.2021.630904
143. Haixu Q. *Study on Bioequivalence and Pharmacokinetics of Cyclosporine a From Three Different Countries in Healthy Chinese Subjects*. 硕士. Dalian Medical University; 2006.
144. Xiao Y, Lv Y, Zhang X, Guo Y, Bergstrom T. The pharmacokinetic and tolerability profile of varenicline in healthy Chinese volunteers. *Int J Clin Pharmacol Ther*. 2009;47(4):246–254. doi:10.5414/cpp47246
145. Zunjian Z, Qiaogen Z, Wei L, Libo Y, Bingren X, Rujin W. Determination of ondansetron in human blood by RP-HPLC. *J Pharm Anal*. 2002;2002(05):386–388.
146. Agoram B, Woltosz WS, Bolger MB. Predicting the impact of physiological and biochemical processes on oral drug bioavailability. *Adv Drug Deliv Rev*. 2001;50 Suppl 1:S41–67. doi:10.1016/s0169-409x(01)00179-x

147. Poulin P, Theil FP. Prediction of pharmacokinetics prior to in vivo studies. 1. Mechanism-based prediction of volume of distribution. *J Pharm Sci*. 2002;91(1):129–156. doi:10.1002/jps.10005
148. Berezhkovskiy LM. Volume of distribution at steady state for a linear pharmacokinetic system with peripheral elimination. *J Pharm Sci*. 2004;93(6):1628–1640. doi:10.1002/jps.20073
149. Jones HM, Parrott N, Jorga K, Lavé T. A novel strategy for physiologically based predictions of human pharmacokinetics. *Clin Pharmacokinet*. 2006;45(5):511–542. doi:10.2165/00003088-200645050-00006
150. UpToDate®. Nurse Pract. 2022;47(10)17. doi: 10.1097/01.NPR.0000873556.24995.ba.
151. Hiemke C. Therapeutic drug monitoring in neuropsychopharmacology: does it hold its promises? *Eur Arch Psychiatry Clin Neurosci*. 2008;258 Suppl 1:21–27. doi:10.1007/s00406-007-1005-y
152. UpToDate.Sertraline Hydrochloride Tablets. Available from: https://www.uptodate.com/contents/packageinsert/38712544-b35b-4222-85e4-6fc12a1dc42c?search=%E8%88%8D%E6%9B%B2%E6%9E%97#. Accessed April 9, 2025.
153. UpToDate.Moclobemide Tablets. Available from: https://www.uptodate.com/contents/packageinsert/ac9cbc3d-2506-4fcd-962d-28d83a087d8f?search=%E5%90%97%E6%B0%AF%E8%B4%9D%E8%83%BA. Accessed April 9, 2025.
154. UpToDate. Alprazolam Tablets. Available from: https://www.uptodate.com/contents/packageinsert/83c115e8-f6d8-402d-901e-0e28649fb956?search=%E9%98%BF%E6%99%AE%E5%94%91%E4%BB%91#useInElderly. Accessed April 9, 2025.
155. UpToDate. Amantadine Hydrochloride Tablets November 17, 2022.
156. Bloomer JC, Ambery C, Miller BE, et al. Identification and characterisation of a salt form of Danirixin with reduced pharmacokinetic variability in patient populations. *Eur J Pharm Biopharm*. 2017;117:224–231. doi:10.1016/j.ejpb.2017.03.023
157. Li Z, Huang G. Table of organ weights for different age groups of Chinese. *J Guangxi Medical College*. 2006;23(1): 155–156. doi:10.16190/j.cnki.45-1211/r.2006.01.088
158. Wang J, Li B, Chen R, et al. Chinese main organ weight reference value. *Chin J Radiol Med Protection*. 1995;4(15): 248–254.
159. Albrecht S, Ihmsen H, Hering W, et al. The effect of age on the pharmacokinetics and pharmacodynamics of midazolam. *Clin Pharmacol Ther*. 1999;65(6):630–639. doi:10.1016/s0009-9236(99)90084-x
160. Nishiyama T, Matsukawa T, Hanaoka K. The effects of age and gender on the optimal premedication dose of intramuscular midazolam. *Anesth Analg*. 1998;86(5):1103–1108. doi:10.1097/00000539-199805000-00038
161. Platten HP, Schweizer E, Dilger K, Mikus G, Klotz U. Pharmacokinetics and the pharmacodynamic action of midazolam in young and elderly patients undergoing tooth extraction. *Clin Pharmacol Ther*. 1998;63(5):552–560. doi:10.1016/s0009-9236(98)90106-0
162. Intravenous Midazolam FDA label. Available from: https://s3-us-west-2.amazonaws.com/drugbank/cite_this/attachments/files/000/002/434/original/Intraveous_Midazolam_FDA_label.pdf?1545435299. Accessed April 9, 2025.
163. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry*. 2018;51(1–02):9–62. doi:10.1055/s-0043-116492

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