


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.

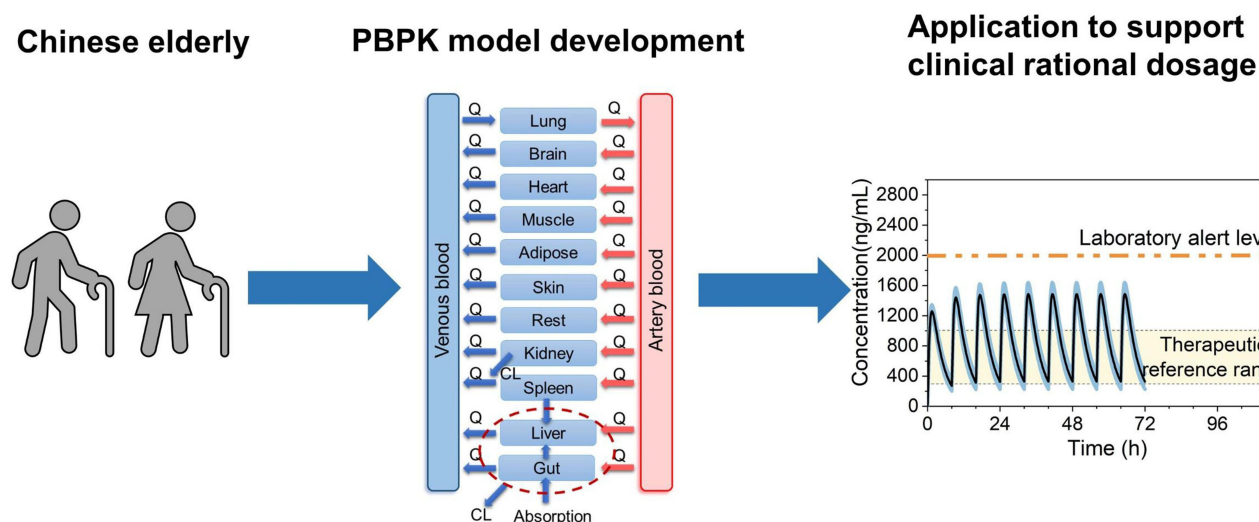
Conclusion: In conclusion, PBPK models for 50 commonly prescribed drugs within the Chinese elderly population were developed, tackling general data gaps associated with these specific medications. Medication plans were developed specifically tailored for the elderly population, presenting an alternative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

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) modeling⁷ 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.

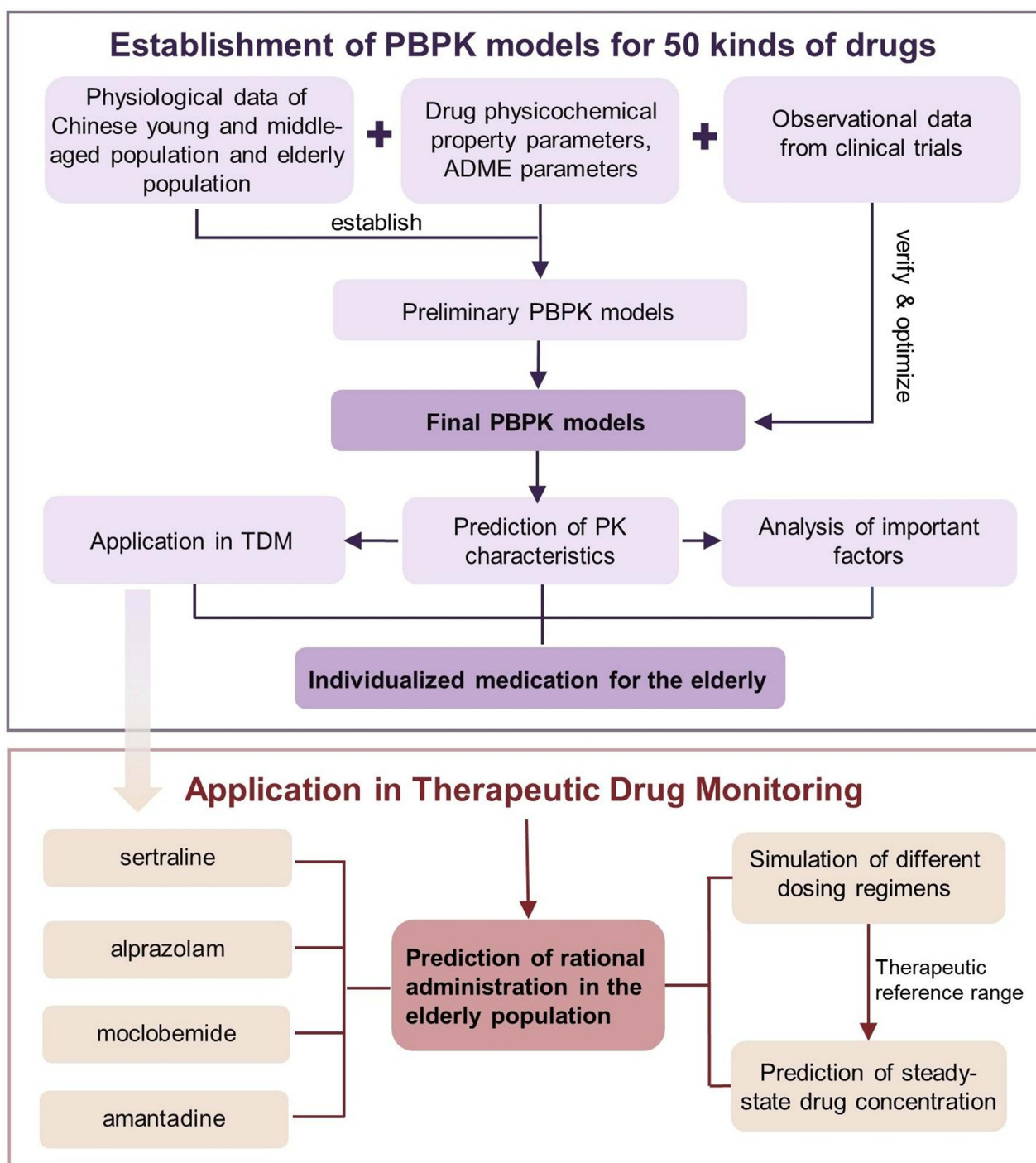


Figure 1 The technical roadmap.

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

(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	
Elaprazole	Drugbank; reference; ¹²⁸ internal data	Internal data	

(Continued)

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 times¹⁴⁹ 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

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
	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
	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)	f _{up}	B:P ratio	K _p *	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)	f _{up}	B:P ratio	K _p *	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
Elaprazole	366.44	4	10.1; 4.27	4.25	0.045	0.5	A	19.61	5.50

(Continued)

Table 5 (Continued).

Drug	mW (g/mol)	logPo:w	pKa	P _{eff} (10 ⁻⁴ cm/s)	f _{up}	B:P ratio	K _p *	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: *K_p 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-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 neuropsychiatric 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 (C_{ss}) 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

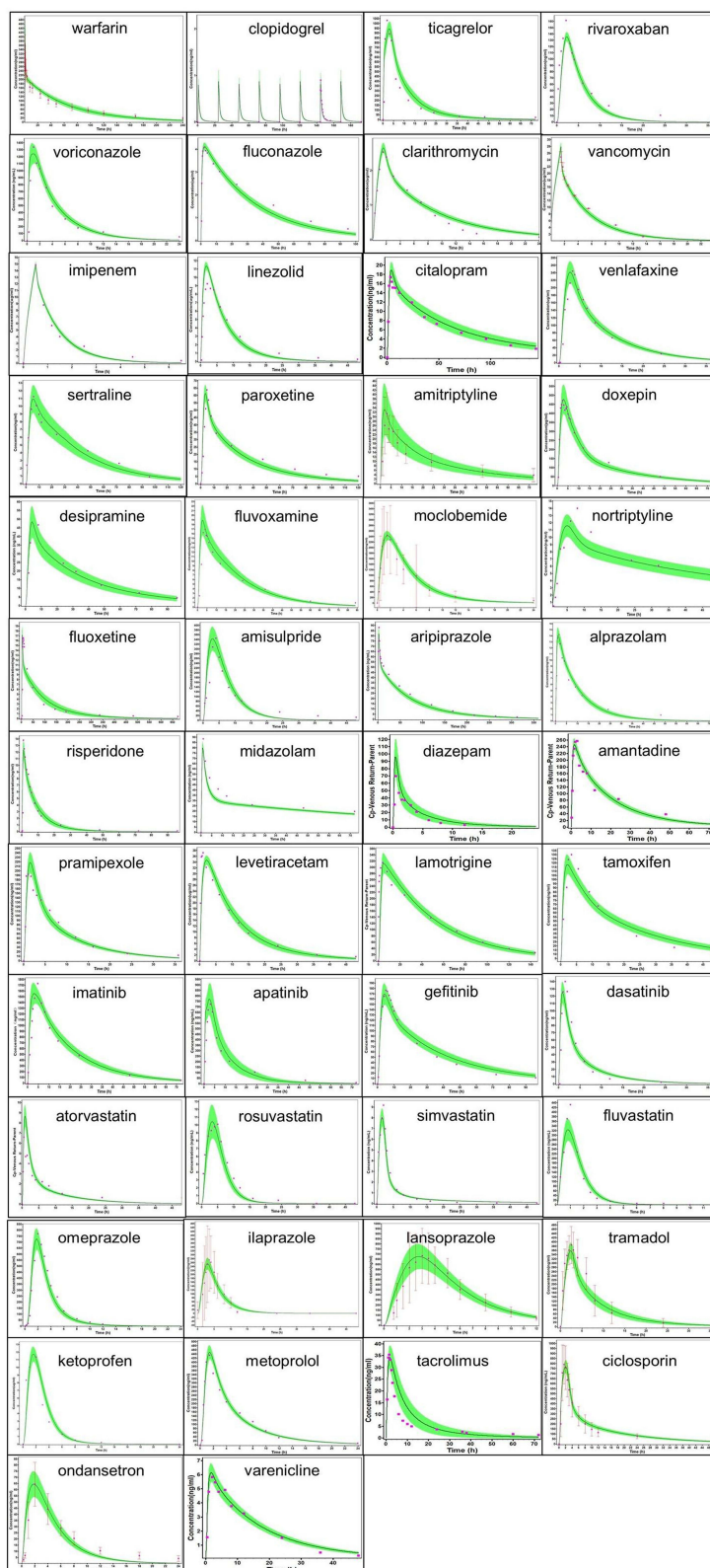


Figure 2 The simulated concentration–time curves of 50 drugs.

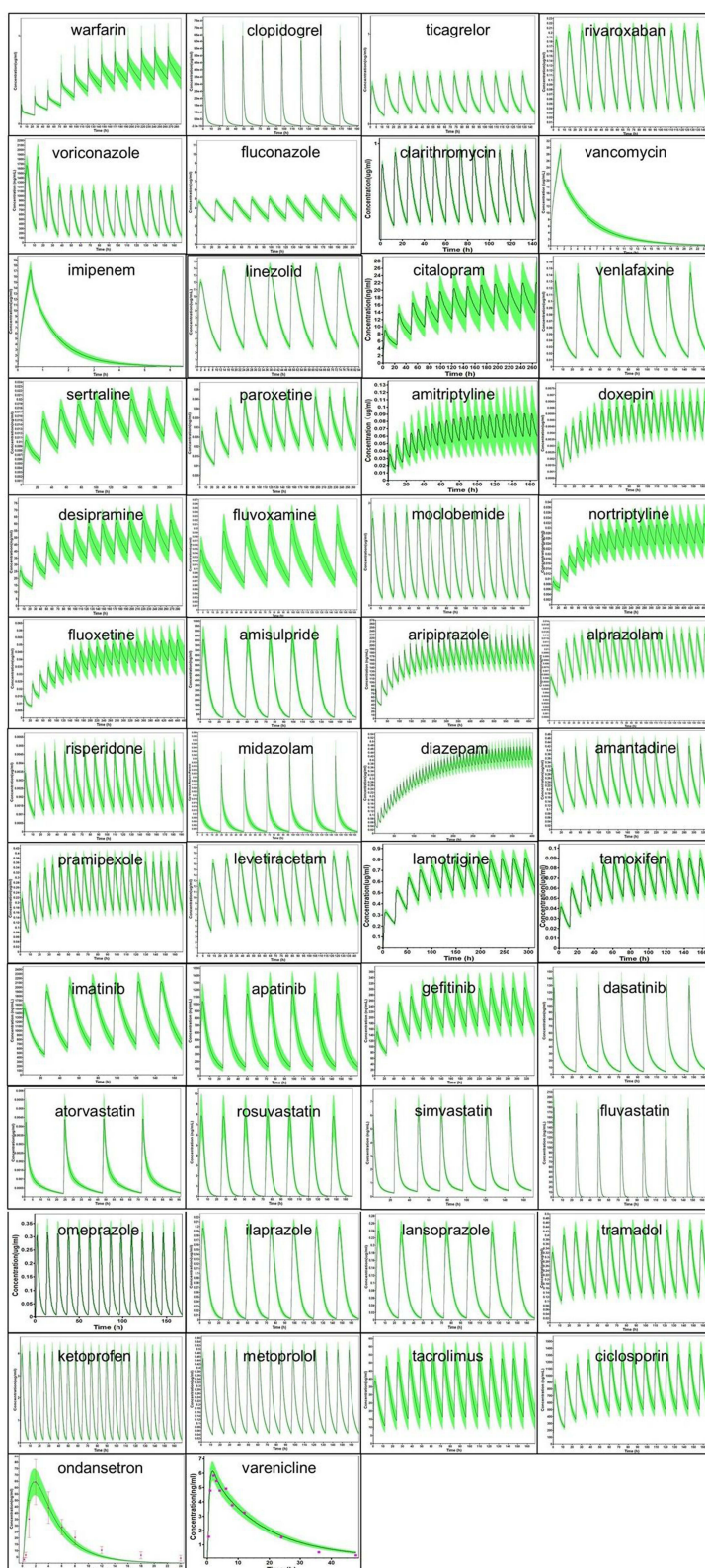


Figure 3 The mean PK characteristics of 50 drugs for the elderly.

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)

Table 6 (Continued).

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

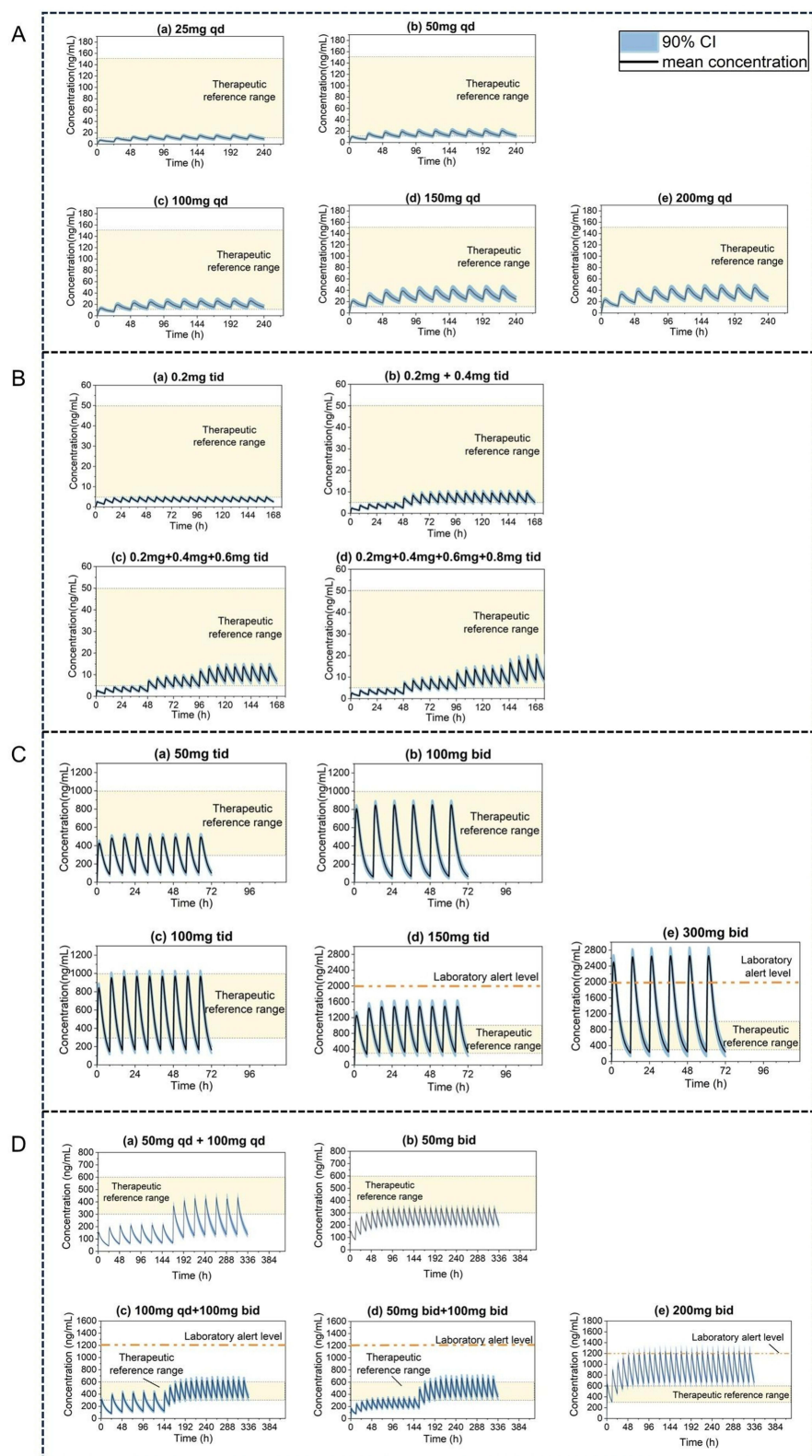


Figure 4 Prediction of pharmacokinetics of four drugs in Chinese elderly population. **(A)** sertraline; **(B)** alprazolam; **(C)** moclobemide; **(D)** amantadine; the black curve represents the predicted mean blood concentration curve, the shaded blue part represents the 90% confidence interval for 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; C_{ss} , steady-state plasma concentration.

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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.

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Disclosure

The authors report no conflicts of interest in this work.

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