

Drug-Drug Interactions and Initial Dosage Optimization of Quetiapine in Patients with Depression: A Real-World Study

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Objective: Quetiapine has been used for treating patients with depression; however, drug-drug interactions (DDIs) deeply limit its individualized administration. This study explored DDIs and initial dose recommendation of quetiapine in depression patients based on real-world data.

Methods: Sixty-four real-world depression patients were used to investigate the effects of drug combinations on quetiapine using a non-linear mixed effect model (NONMEM).

Results: In the final model, paroxetine and fluvoxamine were included as covariates, which significantly affected the clearance rate of quetiapine, with ratios of about 1.00:0.54:0.48:0.26 in patients with depression who were not accompanied by paroxetine or fluvoxamine, patients with depression who were accompanied by paroxetine, patients with depression who were accompanied by fluvoxamine, and patients with depression who were accompanied by paroxetine and fluvoxamine. Furthermore, the initial dose optimizations of quetiapine were 20 and 16 mg/kg/day for depression patients not accompanied by paroxetine or fluvoxamine who weighted 40–80, and 80–120 kg, respectively. The initial dose of quetiapine was 8 mg/kg/day for depression patients accompanied by paroxetine who weighted 40–120 kg. The initial dose of quetiapine was 8 mg/kg/day for depression patients accompanied by fluvoxamine, who weighted 40–120 kg. The initial dose optimization of quetiapine was 4 mg/kg/day for depression patients accompanied by paroxetine and fluvoxamine who weighted 40–120 kg.

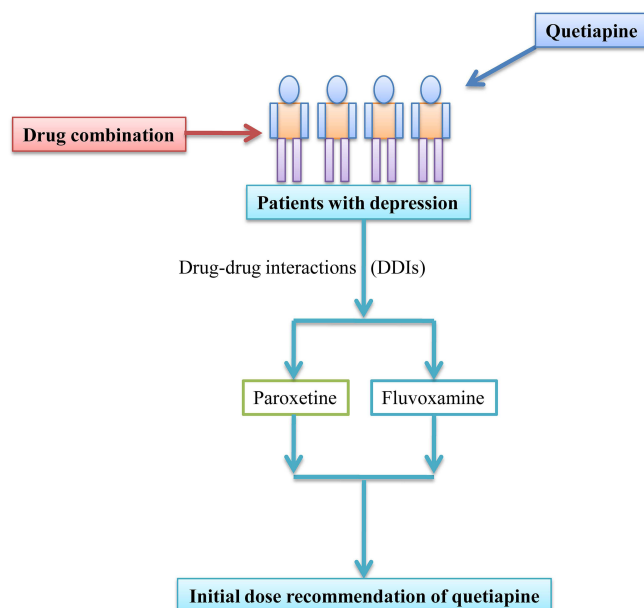
Conclusion: Our study explored DDIs and initial dose recommendation of quetiapine in depression patients from the real world, and the initial dose optimization of quetiapine was recommended based on the interaction with paroxetine or fluvoxamine.

Keywords: drug-drug interactions, initial dose recommendation, quetiapine, depression patients, real world

Introduction

Depression is a mood disorder and demonstrates significant epidemiological features, notably a high prevalence and recurrence rates. It seriously affects physical and mental health, social communication, occupational ability, and physical activity.^{1,2} Epidemiological data indicate a progressive annual increase in depression diagnosis across global populations.^{3–8} The core mechanism of depression includes the imbalance of various neurotransmitter systems, involving the abnormal signaling of monoamine transmitters such as 5-hydroxytryptamine (5-HT) and dopamine (DA), which affect emotional regulation and cognitive function. Clinical management strategies are primarily determined by symptom severity. Mild cases typically respond to psychoeducational interventions, self-management techniques, and psychotherapeutic approaches. In moderate-to-severe cases, pharmacotherapy with antidepressant medications is the primary treatment method.^{9–11}

Graphical Abstract



As an antagonist of several neurotransmitter receptors in the brain, quetiapine is an atypical antipsychotic medication used for treating all schizophrenia variants. Quetiapine regulates neurotransmitter balance and improves mood and cognitive function by antagonizing dopamine D2 and 5-HT_{2A} receptors as well as reducing the emotional symptoms associated with schizophrenia.^{12,13} Evidence supports the role of quetiapine in depression management.^{14–16} However, in the course of treatment for depression, multiple concomitant medications are often used.

Drug-drug interactions (DDIs) are the complex effects of two or more drugs taken by patients simultaneously or within a certain period. These interactions may manifest as either enhanced therapeutic outcomes with reduced adverse effects or conversely diminished efficacy, accompanied by unintended toxicity.^{17,18} Enhanced effects include increased efficacy and increased toxicity, whereas diminished effects include decreased efficacy and decreased toxicity.^{19,20} Optimal clinical management of polypharmacy requires strategic utilization of pharmacological characteristics. The clinical practice process should maximize therapeutic benefits while minimizing adverse reactions by carefully considering the DDIs mechanisms. This approach enhances medication safety and ensures treatment efficacy.^{20,21} On the basis of the principle of occurrence, DDIs can be divided into pharmacodynamic and pharmacokinetic interactions. Pharmacodynamic interactions produce four distinct outcomes: irrelevant, synergistic, additive, and antagonistic. Pharmacokinetic interactions primarily arise from drug-mediated alterations in drug absorption, distribution, metabolism, and excretion.²²

As quetiapine is metabolized by hepatic enzymes, DDIs may affect its metabolism, consequently influencing quetiapine concentrations that directly correlate with therapeutic outcomes and safety assessments.¹⁸ Quetiapine is primarily metabolized by CYP3A4 and CYP2D6,^{23–26} and their inhibition/induction significantly alters drug levels. The therapeutic window of quetiapine in patients was 100–500 ng/mL,²⁷ where subtherapeutic levels risk treatment failure, while supratherapeutic levels increase sedation/QT prolongation risks.

Generally speaking, in the evaluation of DDIs, it is important to check the DDIs database, their reporting, nature, and other features of DDIs. This will provide a systematic way to assess DDIs and their relevance in a clinical scope.^{28,29} DDIs may affect the pharmacokinetics of quetiapine, which in turn affects its concentration, ultimately leading to differences in the real-world need for quetiapine dose for clinical treatment. Population pharmacokinetic (PPK) is a quantitative pharmacological method for studying DDIs and formulating

individualized dose plans.³⁰ Several studies have been conducted on dose recommendation.^{31–37} Thus, this study aimed to explore DDIs and initial dose recommendation of quetiapine in real-world patients with depression via PPK.

Methods

Data Collection

Depression patients treated by quetiapine who were recruited from Xuzhou Oriental Hospital Affiliated to Xuzhou Medical University between March 2021 and January 2024 were included. Inclusion criteria: (a) depression patients, (b) quetiapine treatment, (c) therapeutic drug monitoring for quetiapine. Exclusion criteria: depression patients with missing clinical medical record data. Quetiapine concentrations, relevant medical information of the corresponding patients were collected from real-world clinical practice records. The above research was approved by the Research Ethics Committee of the Xuzhou Oriental Hospital affiliated to Xuzhou Medical University, where the requirement for written informed consent could be waived since the data were collected retrospectively without patient identifiers. This study adhered to the Declaration of Helsinki.

Modeling

A quetiapine PPK model in depression patients was established via non-linear mixed effect modeling (NONMEM), where CL/F, V/F, and Ka (fixed at 1.46/h³⁸) were included.

The inter-individual variability was demonstrated in Formula (i):

$$D_i = TV(D) \times \exp(\eta_i) \quad (i)$$

D_i represents the individual parameters. $TV(D)$ shows typical individual parameters. η_i exhibited a symmetrical distribution.

The random residual variability was demonstrated in Formula (ii):

$$G_i = J_i + J_{i*} \varepsilon_1 + \varepsilon_2 \quad (ii)$$

G_i represents the observed concentrations. J_i demonstrated individual predicted concentrations. ε_1 , ε_2 exhibited symmetrical distributions.

Relationship between weight and pharmacokinetic parameters was demonstrated in Formula (iii):

$$K_i = K_{std} \times (M_i / M_{std})^O \quad (iii)$$

K_i denotes the i th parameters. where M_i represents the i th individual's weight. M_{std} had a 70 kg standard weight and K_{std} had typical individual parameters. O was an allometric coefficients of 0.75 and 1 for CL/F and V/F, respectively.³⁹

Continuous and categorical covariate models are shown in Formulae (iv) and (v), respectively.

$$P_i = TV(P) \times (Q_i / Q_m)^\theta \quad (iv)$$

$$P_i = TV(P) \times (1 + \theta \times Q_i) \quad (v)$$

where P_i is individual parameters. The $TV(P)$ demonstrated typical individual parameters. θ demonstrated parameters for being estimated. where Q_i represents the covariates of i th individual. Q_m represents the median for covariates.

Covariate analysis of the quetiapine PPK model was performed using a stepwise method. The objective function value (OFV) variation was covariate inclusion criteria, among which OFV decrease > 3.84 ($P < 0.05$) was defined as the inclusion standard, and OFV increase > 6.63 ($P < 0.01$) was defined as the exclusion standard.

Model Evaluation

Visualization way and bootstrap were used to evaluate the final quetiapine PPK model.

Simulation

The Monte Carlo method was used to simulate quetiapine concentrations in patients with depression, and the therapeutic window of quetiapine in these patients was 100–500 ng/mL.²⁷ In addition, paroxetine and fluvoxamine, which significantly affected the clearance rate of quetiapine in depression patients, were included as covariates. To determine whether paroxetine or fluvoxamine were co-administered, we simulated four different cases: (a) patients with depression who were not accompanied by paroxetine or fluvoxamine; (b) patients with depression who were accompanied by paroxetine; (c) patients with depression who were accompanied by fluvoxamine; and (d) patients with depression who were accompanied by paroxetine and fluvoxamine. Each case simulated thousand virtual patients with depression, with five different weight groups (40, 60, 80, 100, and 120 kg) and eight different dose groups (1, 4, 8, 12, 16, 20, 24, and 28 mg/kg/day). The probability of attaining a therapeutic concentration range was chosen as the evaluation criterion, and the upper limit of the therapeutic concentration indicated that when the concentration of the drug in the blood reached an upper limit, it may reduce the tolerance of the drug, increase the adverse reactions, or the therapeutic effect would no longer increase or even decrease. Therefore, we evaluated the probability of exceeding the ceiling of the therapeutic concentration (500 ng/mL) at thousand simulated concentrations as a secondary evaluation index.

Results

Patient Information

Sixty-four depression patients treated with quetiapine were included for analysis, where 24 men and 40 women, whose ages were 23.29 ± 13.79 years old, weights were 65.35 ± 16.63 kg. Relevant medical information is shown in Tables 1 and 2, respectively.

Table 1 Demographic Data of Patients with Depression (n = 64)

Characteristic	Mean $\pm$ SD	Median (Minimum-Maximum)
Gender (men/women)	24/40	/
Age (years)	23.29 ± 13.79	17.05 (12.05–65.29)
Weight (kg)	65.35 ± 16.63	65.00 (39.00–117.00)
Albumin (g/L)	41.80 ± 3.01	41.75 (35.80–49.50)
Globulin (g/L)	25.62 ± 2.67	25.70 (18.90–32.80)
Alanine transaminase (IU/L)	31.58 ± 30.04	22.50 (5.00–190.00)
Aspartate transaminase (IU/L)	24.79 ± 15.47	19.00 (12.00–94.00)
Creatinine (μ mol/L)	59.98 ± 12.63	60.50 (34.00–92.00)
Urea (mmol/L)	4.10 ± 1.06	4.06 (1.62–7.06)
Total protein (g/L)	67.42 ± 3.92	67.05 (57.70–75.70)
Total cholesterol (mmol/L)	4.51 ± 0.90	4.34 (2.69–7.04)
Triglyceride (mmol/L)	1.81 ± 0.97	1.61 (0.54–6.23)
Direct bilirubin (μ mol/L)	1.92 ± 0.95	1.75 (0.50–5.90)
Total bilirubin (μ mol/L)	6.81 ± 2.96	6.05 (2.00–19.60)
Hematocrit (%)	39.34 ± 4.26	38.30 (31.40–47.90)
Hemoglobin (g/L)	130.51 ± 16.01	127.00 (104.00–164.00)

(Continued)

Table 1 (Continued).

Characteristic	Mean $\pm$ SD	Median (Minimum-Maximum)
Mean corpuscular hemoglobin (pg)	29.46 $\pm$ 1.72	29.40 (24.90–33.00)
Mean corpuscular hemoglobin concentration (g/L)	331.34 $\pm$ 9.43	331.00 (310.00–351.00)

Table 2 Drug Combination in Patients with Depression (n = 64)

Drug	N
Alprazolam tablets	7
Atorvastatin calcium tablets	1
Chlorpromazine hydrochloride tablets	1
Clonazepam tablets	29
Fluvoxamine maleate tablets	4
Haloperidol injection	2
Lamotrigine tablets	1
Lithium carbonate sustained-release tablets	19
Lorazepam tablets	6
Metformin hydrochloride tablets	1
Metoprolol succinate sustained-release tablets	1
Olanzapine tables	1
Paroxetine hydrochloride tablets	5
Propranolol hydrochloride tablets	4
Sertraline hydrochloride tables	34
Silymarin capsules	2
Sodium valproate sustained-release tablets	12
Sodium valproate tablets	5
Trihexyphenidyl hydrochloride tablets	2
Venlafaxine hydrochloride sustained-release capsules	3
Zopiclone tablets	3

Note: N, number of patients receiving concomitant medications.

Modeling

The drug interaction evaluation process for quetiapine in depression patients was presented in [Table S1](#). Paroxetine and fluvoxamine were included as covariates, which significantly affected the clearance rate of quetiapine, with ratios of about 1.00:0.54:0.48:0.26 in patients with depression who were not accompanied by paroxetine or fluvoxamine, patients with depression who were accompanied by paroxetine, patients with depression who were accompanied by fluvoxamine, and patients with depression who were accompanied by paroxetine and fluvoxamine. PPK model was as follows:

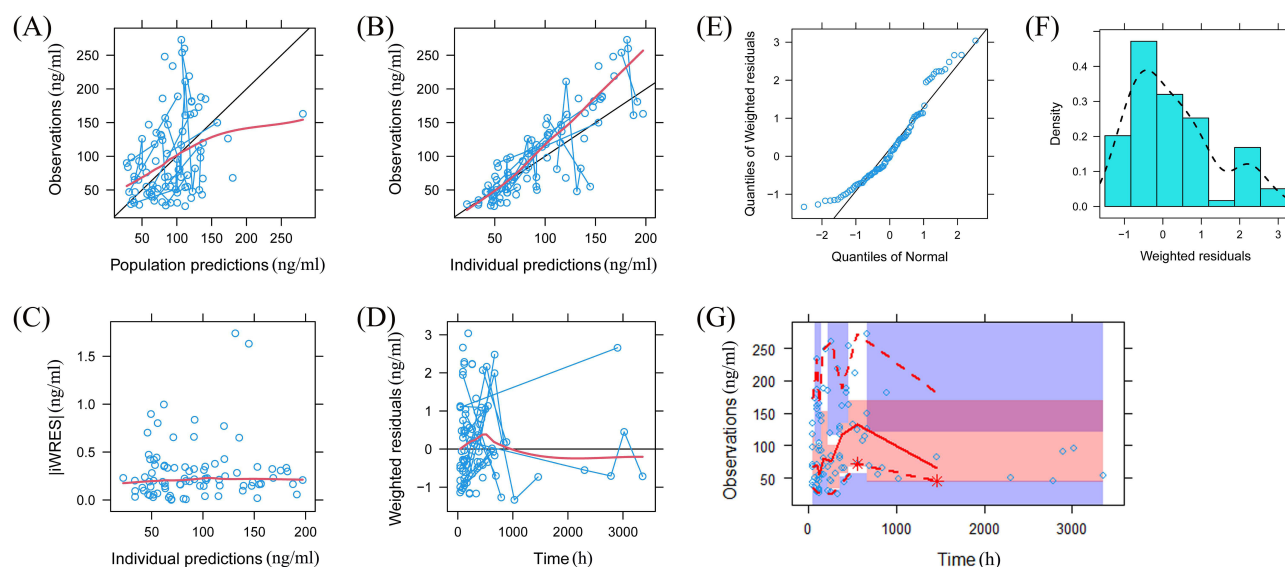


Figure 1 Model evaluation. **(A)** Observations vs population predictions. **(B)** Observations vs individual predictions. **(C)** absolute value of weighted residuals of individual ($|iWRES|$) vs individual predictions. **(D)** Weighted residuals vs time. **(E)** Quantiles of weighted residuals vs quantiles of normal. **(F)** Density vs weighted residuals. **(G)** Visual predictive check (VPC) of model. * $P < 0.05$.

$$CL/F = 141 \times (\text{weight}/70)^{0.75} \times (1 - 0.460 \times \text{PAR}) \times (1 - 0.518 \times \text{FLU}) \quad (\text{vi})$$

$$V/F = 1460 \times (\text{weight}/70) \quad (\text{vii})$$

PAR was administered as paroxetine, and FLU as fluvoxamine. When patients with depression received paroxetine or fluvoxamine, PAR or FLU was 1; If not, PAR or FLU was 0.

Evaluation

Figure 1 showed a visual evaluation of the quetiapine PPK model in patients with depression. Figure 2 showed the individual plots. Table 3 showed bootstrap validation. The above results indicated that final quetiapine PPK model was accurate and reliable.

Recommended Dose

We simulated four different cases: (a) patients with depression who were not accompanied by paroxetine or fluvoxamine, (b) patients with depression who were accompanied by paroxetine, (c) patients with depression who were accompanied by fluvoxamine, and (d) patients with depression who were accompanied by paroxetine and fluvoxamine, as shown in Figures 3–6, respectively. The probability of attaining a therapeutic concentration range of quetiapine in depression patients was shown in Figure 7. Figure 7A–D represent patients with depression who were not accompanied by paroxetine or fluvoxamine, patients with depression who were accompanied by paroxetine, patients with depression who were accompanied by fluvoxamine, and patients with depression who were accompanied by paroxetine and fluvoxamine, respectively.

The initial dose recommendation of quetiapine in depression patients was shown in Table 4, in which the initial dose optimizations of quetiapine were 20 and 16 mg/kg/day for patients with depression not accompanied with paroxetine or fluvoxamine, who weighted 40–80, and 80–120 kg, respectively, and the probability of attaining a therapeutic concentration range for the doses of 20 and 16 mg/kg/day was 83.2–87.2%, 87.2–88.9%, respectively. The initial dose optimization of quetiapine was 8 mg/kg/day for depression patients accompanied by paroxetine, who weighted 40–120 kg, and the probability of attaining a therapeutic concentration range for a dose of 8 mg/kg/day was 92.6–97.1%. The initial dose optimization of quetiapine was 8 mg/kg/day for depression patients accompanied by fluvoxamine, who weighted 40–120 kg, and the probability of attaining a therapeutic concentration range for a dose of

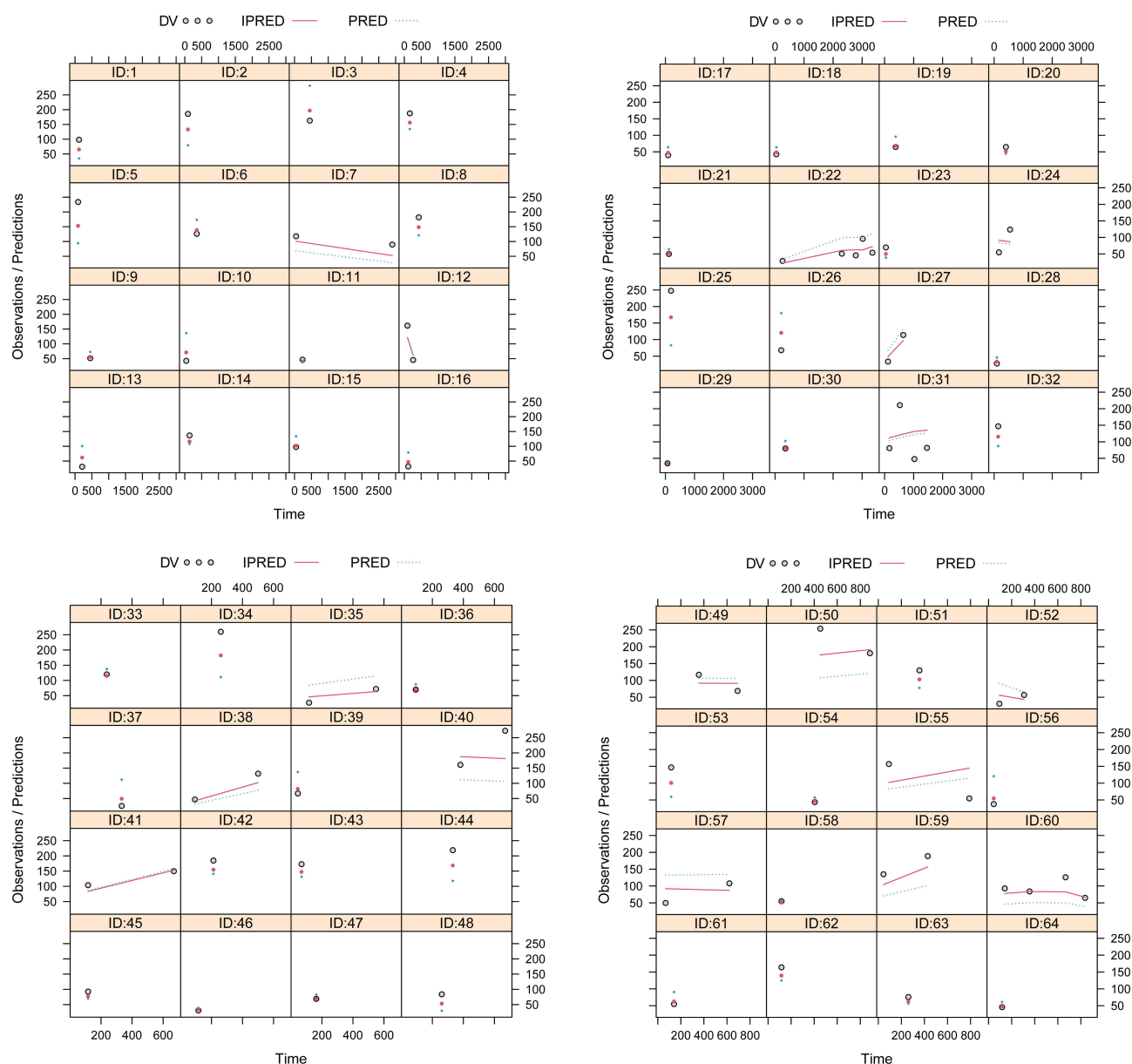


Figure 2 Individual plots. ID: patient ID number. Gray dot: DV, measured concentration. Red line or red dot (when the patient had only one concentration point): IPRED, Individual predictive value. Blue line or blue dot (when the patient had only one concentration point): PRED, Population predictive value.

8 mg/kg/day was 94.4–97.0%. The initial dose optimization of quetiapine was 4 mg/kg/day for depression patients accompanied by paroxetine and fluvoxamine, who weighted 40–120 kg, and the probability of attaining a therapeutic concentration range for a dose of 4 mg/kg/day was 98.9–99.8%.

Secondary Evaluation Index

The probability of more than ceiling of the therapeutic concentration (500 ng/mL) at thousand simulated concentrations was used as a secondary evaluation index, as shown in Figure 8, where Figure 8A–D show patients with depression who were not accompanied by paroxetine or fluvoxamine, patients with depression who were accompanied with paroxetine, patients with depression who were accompanied with fluvoxamine, and patients with depression who were accompanied with paroxetine and fluvoxamine, respectively. For patients with depression who were not accompanied by paroxetine or fluvoxamine, the probability of exceeding ceiling of the therapeutic concentration was 2.8–7.5% and 2.6–5.2% for the initial dose optimization of quetiapine at 20 and 16 mg/kg/day, respectively. For patients with depression who were

Table 3 Parameter Estimates of Quetiapine Final Model and Bootstrap Validation in Patients with Depression

Parameter	Estimate	SE (%)	Bootstrap		Bias (%)
			Median	90% Confidence Interval	
CL/F (L/h)	141	19.7	118	[10, 166]	−16.31
V/F (L)	1460	53.5	1060	[23, 2468]	−27.40
K _a (h ^{−1})	1.46 (fixed)	–	–	–	–
θ _{PAR}	−0.460	29.8	−0.322	[−0.637, −0.090]	−30.00
θ _{FLU}	−0.518	43.4	−0.350	[−0.748, −0.034]	−32.43
ω _{CL/F}	0.322	28.1	0.198	[0.058, 0.401]	−38.51
σ ₁	0.365	18.7	0.358	[0.236, 0.462]	−1.92
σ ₂	15.199	50.2	12.787	[0.080, 31.819]	−15.87

Notes: A 90% confidence interval is displayed as the 5th and 95th percentiles of the bootstrap estimates. CL/F, apparent oral clearance (L/h); V/F, apparent volume of distribution (L); K_a, absorption rate constant (h^{−1}); θ_{PAR}, θ_{FLU} are the coefficients of paroxetine and fluvoxamine, respectively; ω_{CL/F}, inter-individual variability of CL/F; σ₁, residual variability, proportional error; σ₂, residual variability, additive error; bias, prediction error; bias = (median−estimate)/estimate × 100%.

accompanied with paroxetine, the probability to more than ceiling of the therapeutic concentration was 0.2–2.3% for the initial dose optimization of quetiapine of 8 mg/kg/day. For patients with depression who were accompanied with fluvoxamine, the probability to more than ceiling of the therapeutic concentration was 0.8–5.1% for the initial dose optimization of quetiapine of 8 mg/kg/day. For patients with depression accompanied by paroxetine and fluvoxamine, the probability of exceeding ceiling of the therapeutic concentration was 0 for the initial dose optimization of quetiapine at 4 mg/kg/day. The results were presented in Table 4.

Discussion

In clinical practice, pharmacokinetic interactions are frequently a source of DDIs. These interactions occur primarily when perpetrator drugs alter the activity of metabolic enzymes or transporters responsible for victim drug processing, leading to variable pharmacokinetic characteristics.^{40–44} Serious DDIs can significantly affect real-world patient care and optimal dose recommendation.^{45,46}

Therefore, we constructed a PPK model of quetiapine in patients with depression by integrating real-world combination therapy data. This quantitative pharmacological framework specifically examined the effects of DDIs on quetiapine metabolism in patients with depression. This study aimed to screen out potential combined administration information affecting quetiapine clearance and recommend a precise quetiapine administration regimen for patients with depression. This study relied on clinical records, and the feasibility of relying on clinical records for DDIs analysis has been demonstrated in previous researches.^{47–49}

Sixty-four real-world patients with depression were used to investigate the effects of DDIs on quetiapine using NONMEM. Of course, since this study was derived from sparse data in the real world, the information density was insufficient, which would have a certain impact on the stability of the PPK model. This was an objective characteristic of sparse data in the real world. However, judging from the published research, this influence had a limited impact on our main results. For example, in our study, the CL/F of quetiapine in patients with depression was 141 L/h, similar to the CL/F of quetiapine in patients with schizophrenia.³⁰ In addition, the allometric scaling method was adopted in this study. The fixed inclusion of body weight as a core physiological covariate enabled the PPK model to have both individualized accuracy and clinical practicability. It not only supported the scientific transformation from a fixed dose to a weight gradient dose but also provided a basis for dynamic dose adjustment for patients with special physiological states. This kind of research had been reported in a considerable number of relevant literatures.^{50–52}

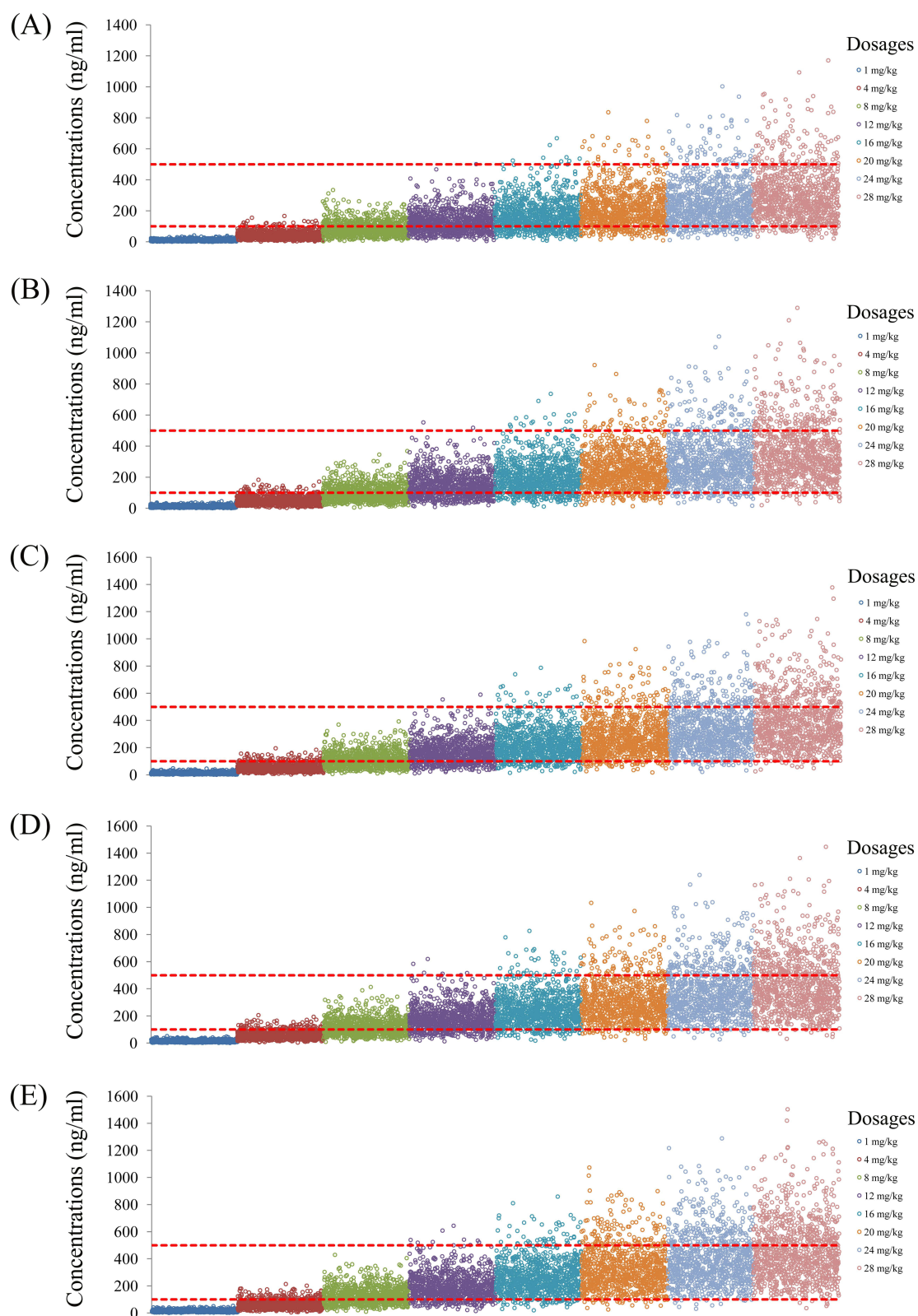


Figure 3 The simulated quetiapine concentrations of patients with depression who were not accompanied with paroxetine or fluvoxamine. **(A)** Patients with depression weighted 40 kg. **(B)** Patients with depression weighted 60 kg. **(C)** Patients with depression weighted 80 kg. **(D)** Patients with depression weighted 100 kg. **(E)** Patients with depression weighted 120 kg.

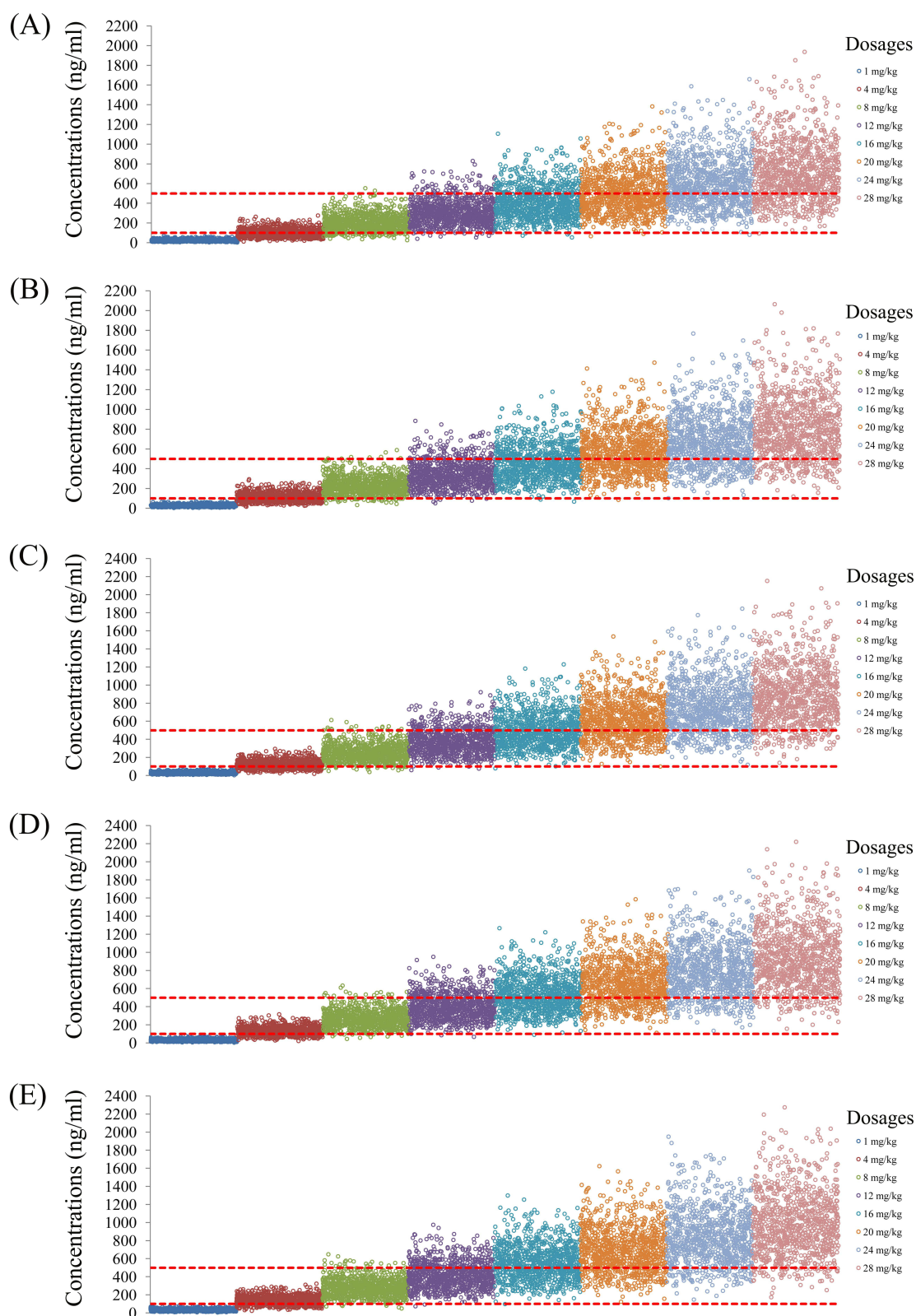


Figure 4 The simulated quetiapine concentrations of patients with depression who were accompanied with paroxetine. **(A)** Patients with depression weighted 40 kg. **(B)** Patients with depression weighted 60 kg. **(C)** Patients with depression weighted 80 kg. **(D)** Patients with depression weighted 100 kg. **(E)** Patients with depression weighted 120 kg.

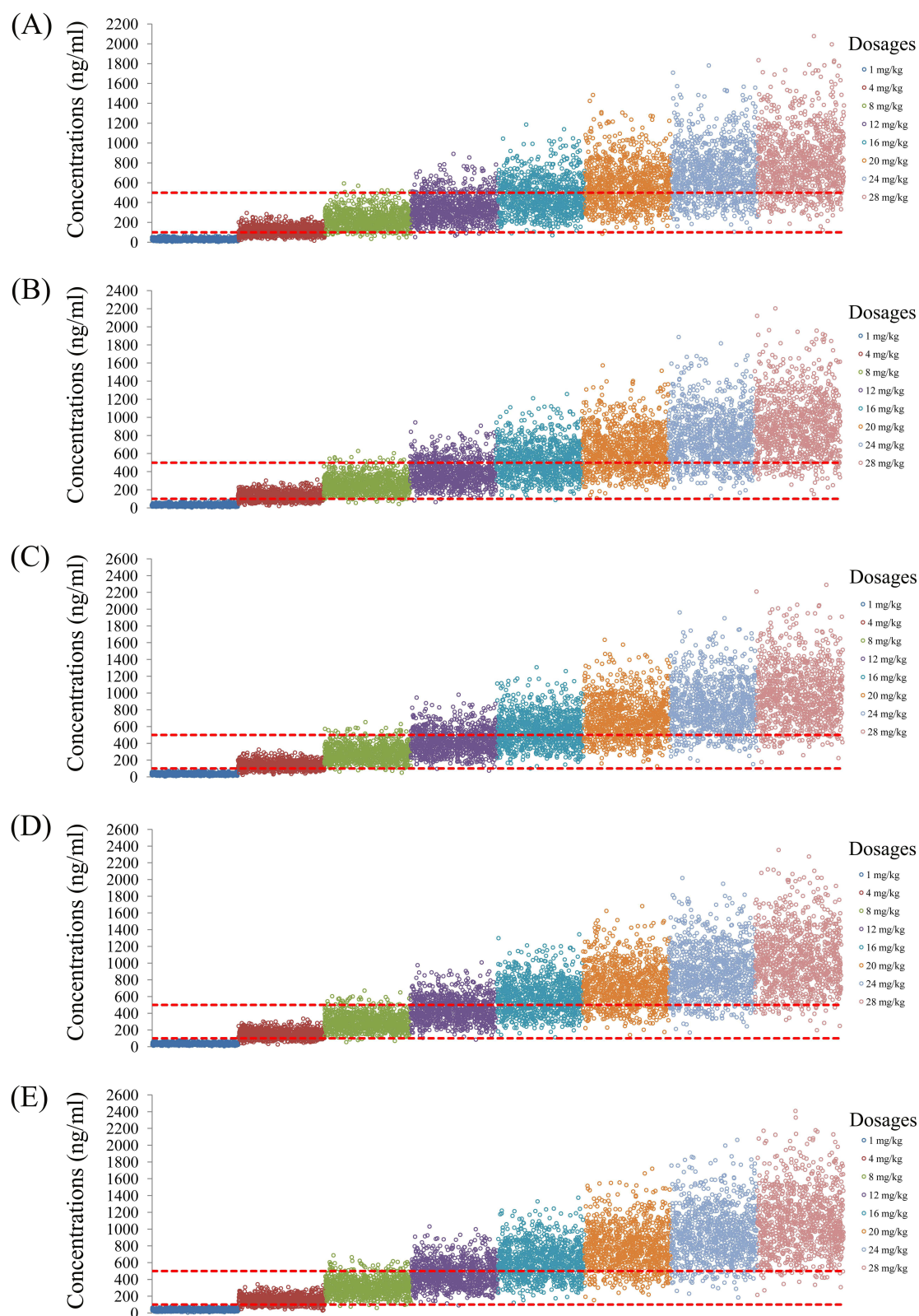


Figure 5 The simulated quetiapine concentrations of patients with depression who were accompanied with fluvoxamine. (A) Patients with depression weighted 40 kg. (B) Patients with depression weighted 60 kg. (C) Patients with depression weighted 80 kg. (D) Patients with depression weighted 100 kg. (E) Patients with depression weighted 120 kg.

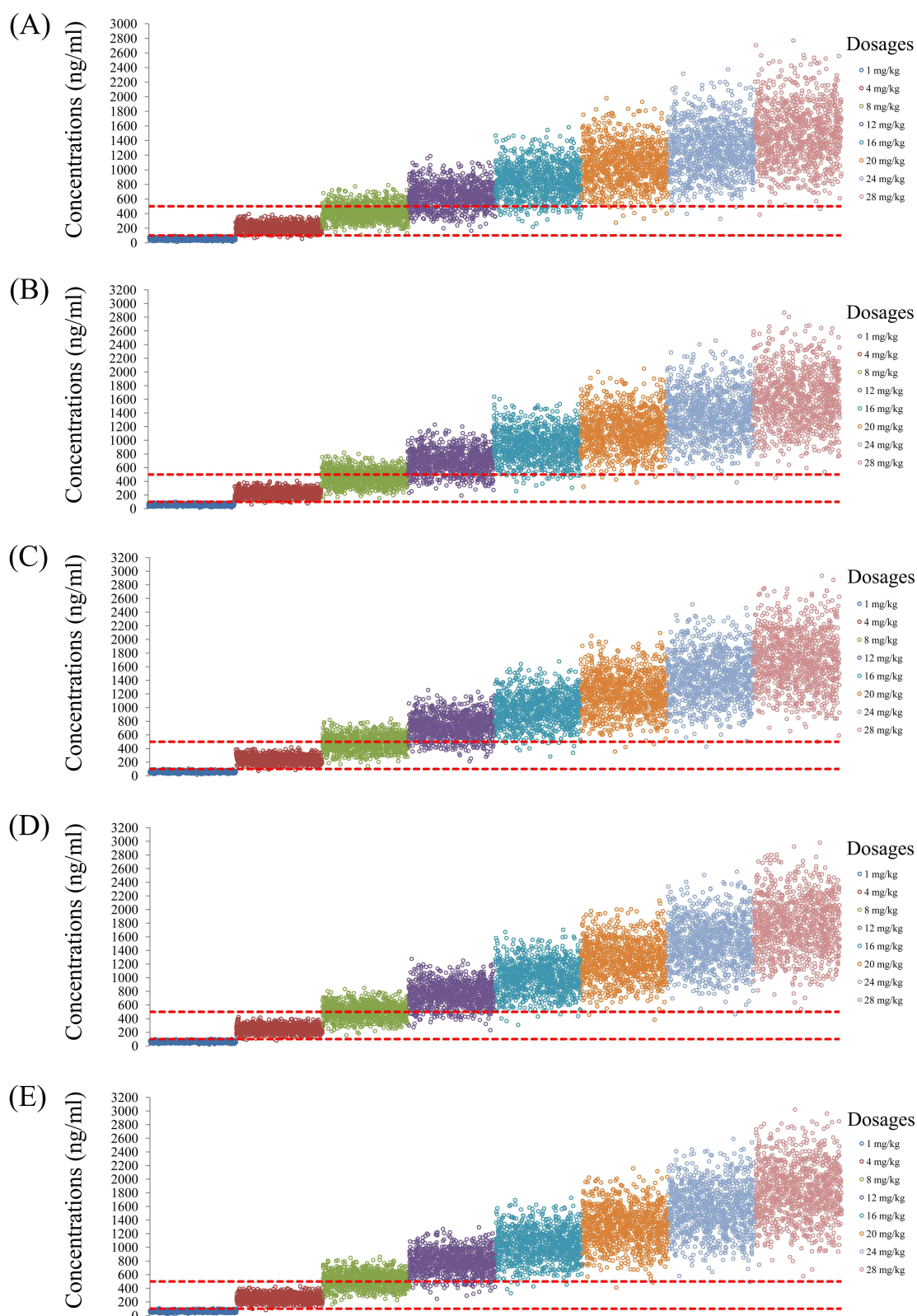


Figure 6 The simulated quetiapine concentrations of patients with depression who were accompanied with paroxetine and fluvoxamine. **(A)** Patients with depression weighted 40 kg. **(B)** Patients with depression weighted 60 kg. **(C)** Patients with depression weighted 80 kg. **(D)** Patients with depression weighted 100 kg. **(E)** Patients with depression weighted 120 kg.

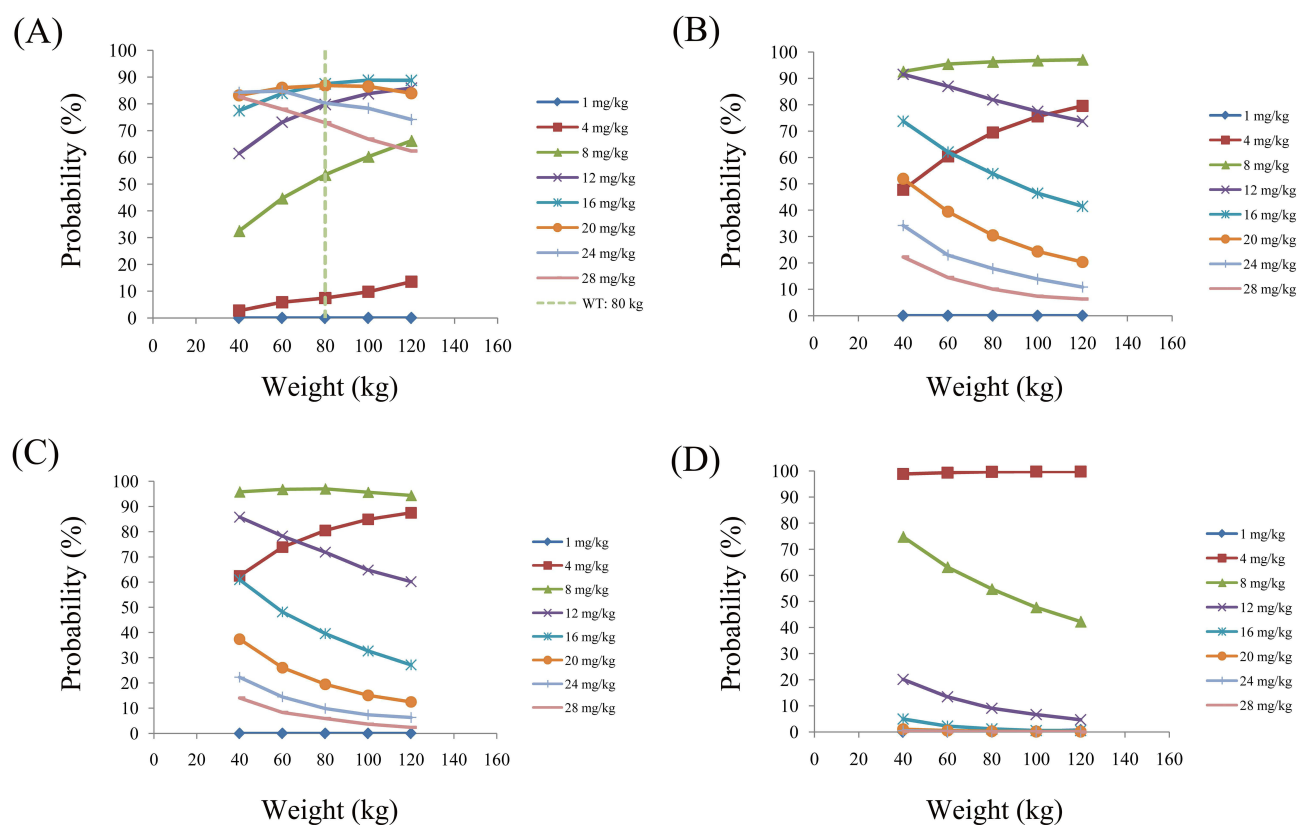


Figure 7 Probability to achieve the target concentrations of quetiapine in patients with depression. **(A)** Patients with depression who were not accompanied with paroxetine or fluvoxamine. **(B)** Patients with depression who were accompanied with paroxetine. **(C)** Patients with depression who were accompanied with fluvoxamine. **(D)** Patients with depression who were accompanied with paroxetine and fluvoxamine.

The combined medications analyzed in this study included alprazolam tablets, atorvastatin calcium tablets, chlorpromazine hydrochloride tablets, clonazepam tablets, fluvoxamine maleate tablets, haloperidol injection, lamotrigine tablets, lithium carbonate sustained-release tablets, lorazepam tablets, metformin hydrochloride tablets, metoprolol succinate sustained-release tablets, olanzapine tablets, paroxetine hydrochloride tablets, propranolol hydrochloride tablets, sertraline

Table 4 Initial Dose Recommendation of Quetiapine in Patients with Depression

Without Paroxetine				With Paroxetine			
Without fluvoxamine				Without fluvoxamine			
Body weight (kg)	Dose (mg/kg/day)	Probability to achieve the target concentrations (%)	Probability to exceed the upper limit of the target concentrations (%)	Body weight (kg)	Dose (mg/kg/day)	Probability to achieve the target concentrations (%)	Probability to exceed the upper limit of the target concentrations (%)
[40–80]	20	83.2–87.2	2.8–7.5	[40–120]	8	92.6–97.1	0.2–2.3
[80–120]	16	87.2–88.9	2.6–5.2				
With fluvoxamine				With fluvoxamine			
Body weight (kg)	Dose (mg/kg/day)	Probability to achieve the target concentrations (%)	Probability to exceed the upper limit of the target concentrations (%)	Body weight (kg)	Dose (mg/kg/day)	Probability to achieve the target concentrations (%)	Probability to exceed the upper limit of the target concentrations (%)
[40–120]	8	94.4–97.0	0.8–5.1	[40–120]	4	98.9–99.8	0

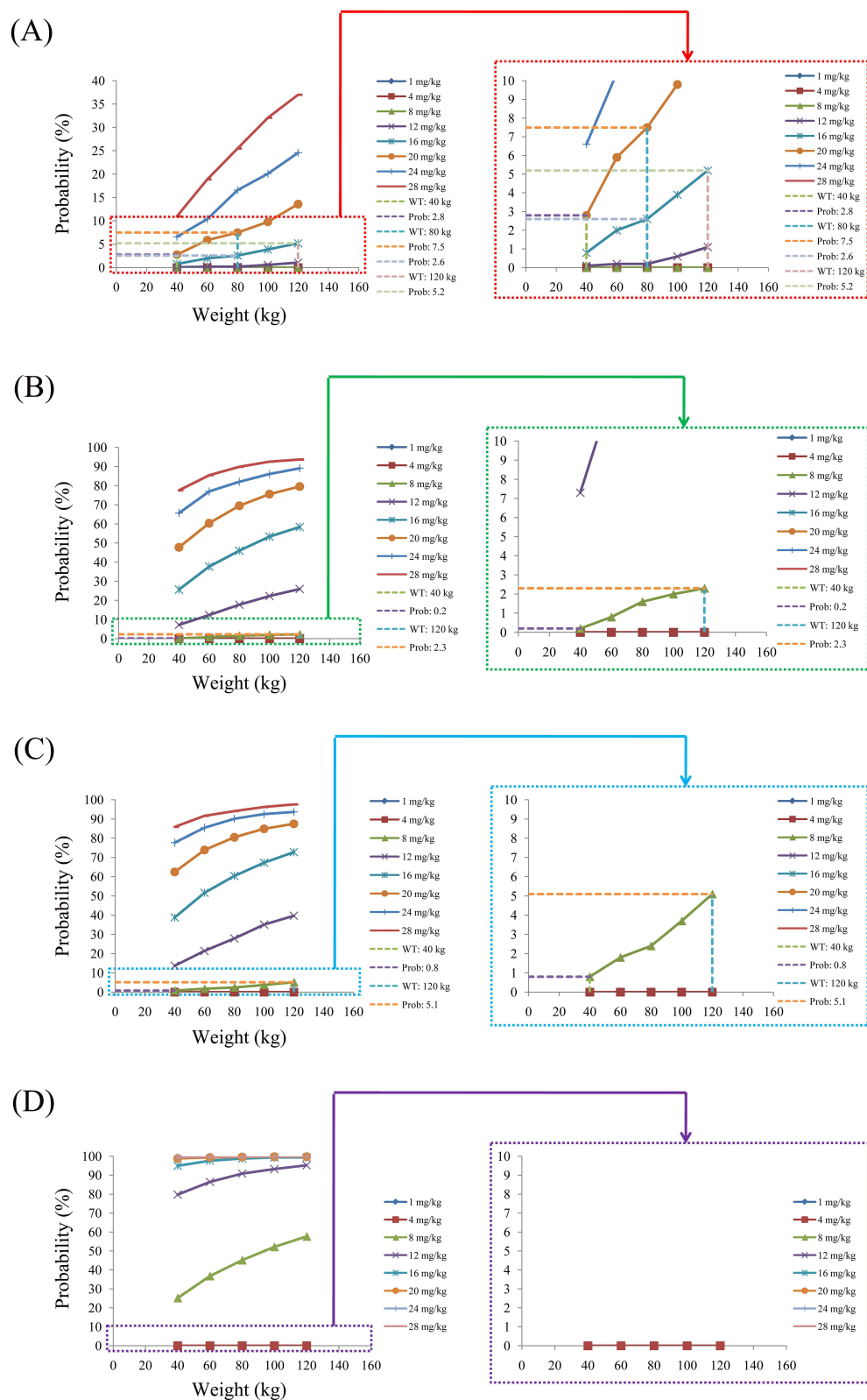


Figure 8 Probability to exceed the upper limit of the target concentrations of quetiapine in patients with depression. **(A)** Patients with depression who were not accompanied with paroxetine or fluvoxamine. **(B)** Patients with depression who were accompanied with paroxetine. **(C)** Patients with depression who were accompanied with fluvoxamine. **(D)** Patients with depression who were accompanied with paroxetine and fluvoxamine.

hydrochloride tablets, silymarin capsules, sodium valproate sustained-release tablets, sodium valproate tablets, trihexyphenidyl hydrochloride tablets, venlafaxine hydrochloride sustained-release capsules, zopiclone tablets.

The final PPK model identified paroxetine and fluvoxamine as significant covariates influencing quetiapine clearance in patients with depression. When patients with depression received paroxetine simultaneously, quetiapine clearance decreased by 46.0%, and when patients with depression received fluvoxamine, quetiapine clearance decreased by 51.8%. Decreased clearance can lead to the accumulation of quetiapine, and higher quetiapine concentrations can lead to consciousness and movement disorders, nervous function abnormalities, metabolic disorders, endocrine abnormalities, etc. This is mainly because quetiapine is primarily metabolized by CYP3A4 and CYP2D6,^{23–26} however paroxetine is an inhibitor of CYP2D6^{53,54} and fluvoxamine is an inhibitor of CYP3A4.^{55–57} Furthermore, optimized initial doses of quetiapine are recommended in patients with depression. This study replenishes quetiapine DDIs in a real-world setting. When patients with depression take paroxetine or fluvoxamine simultaneously, individualized doses of quetiapine could be guided more accurately and conveniently, according to the study.

However, since the present study was a single-center retrospective and small sample size real-world study. The population consisted of patients with depression from China. In addition, the limited number of patients co-administered with paroxetine and fluvoxamine. Therefore, in future studies, we need to optimize the sampling design (such as dense sampling), enhance the integrity of collection, and increase the number of enrolled patients via multicenter prospective study.

Conclusion

Our study explored DDIs and initial dose optimization of quetiapine in patients with depression from the real world for the first time, and the initial dose optimization of quetiapine was recommended based on the interaction with paroxetine or fluvoxamine.

Data Sharing Statement

The de-identified participant data will be made available upon reasonable request to the corresponding author. Available data includes individual participant records that support the published findings, with appropriate measures in place to maintain participant confidentiality according to established research ethics guidelines.

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Disclosure

Xiao Chen, Yue Zhang, Di Yin and Ying-Wei Jin are co-first authors. The authors have no conflict of interest to disclose.

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