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ORIGINAL RESEARCH

Drug–Drug Interactions and Individualized Clozapine Therapy in Patients with Depression: Insights from Real-World Data

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Objective: Clozapine is widely used in patients with depression but its metabolism via multiple hepatic enzymes raises concerns about drug–drug interactions (DDIs). The extent of these interactions in real-world clinical settings remains unclear.

Methods: This research involved 29 patients with depression from the real world, utilizing their clozapine concentration data, physiological and biochemical data, and drug combination data to construct a DDI evaluation model using the population pharmacokinetics (PPK) method and NONMEM software.

Results: The results of our research reveal that fluvoxamine maleate has a noteworthy DDI with clozapine, and fluvoxamine reduced clozapine clearance by 56.5%, necessitating substantial dose reductions. Furthermore, clozapine doses of 9 mg/kg, 8 mg/kg, 7 mg/kg and 6 mg/kg are recommended for 40–47 kg, 47–70 kg, 70–100 kg and 100–120 kg patients with depression not takingw fluvoxamine maleate, respectively. Clozapine doses of 3 mg/kg and 2 mg/kg are recommended for 40–70 kg and 70–120 kg patients with depression taking fluvoxamine maleate, respectively.

Conclusion: This study provides the first real-world evidence to guide safe and individualized clozapine dosing in patients with depression, particularly in the context of fluvoxamine co-administration. When patients with depression patient are treated with fluvoxamine maleate, the dosage of clozapine needs to be reduced.

Keywords: drug–drug interactions, individualized therapy, clozapine, depression, real-world

Introduction

Depression, also known as depressive disorder, is a highly prevalent mental disorder.[1] It can be significant and persistent. Some patients may self-harm or exhibit suicidal behavior, and may even have psychotic symptoms such as delusions and hallucinations. In clinical practice, depression can be classified into mild, moderate and severe based on the number, type and severity of symptoms. Depression is mainly characterized by low mood, loss of interest and lack of energy. There are also some early symptoms such as slow response, slow thinking and memory decline, but these may vary among individuals. Depression is not contagious, but it is closely related to stressful life events, pessimistic personality traits, history of other mental illnesses, severe chronic diseases, drug and alcohol abuse, and so on.[2–8]

The treatment of depression mainly includes drug therapy, psychotherapy and physical therapy. Drug therapy is the main treatment method, where the main drugs for depression include fluoxetine, paroxetine, sertraline, citalopram, fluvoxamine, escitalopram, venlafaxine and duloxetine.[8–17] When patients with depression experience delusions (such as self-guilt delusions or nihilistic delusions) or hallucinations consistent with their emotions, clozapine can be used in combination with antidepressants to alleviate psychotic symptoms and improve the depressive state.[18–26] Furthermore, recent work suggests tht clozapine has an antidepressant effect too.[27] Clozapine is mainly metabolized by cytochrome

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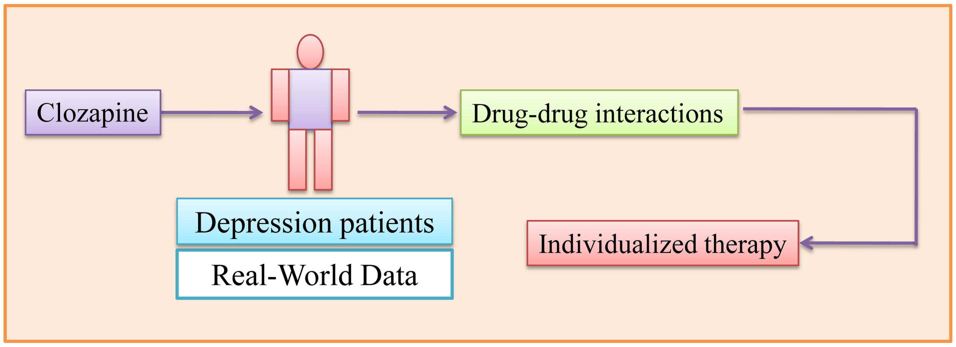
Graphical Abstract



P450 (CYP) enzymes in liver cells. Among these, CYP1A2 and CYP3A4 are the main metabolic enzymes, leading to an increased likelihood of CYP enzyme-mediated drug–drug interactions (DDI).

Real-world data falls within the scope of real-world research and refers to the collection of multi-source heterogeneous medical data generated in daily medical practice. Unlike traditional clinical trials, real-world data is derived from the routine diagnosis and treatment process, and it reflects the status and treatment outcomes of patients in real diagnosis and treatment scenarios.[28–31]

However, it remains unclear whether clozapine will result in DDI when combined with other therapeutic drugs during clinical treatment. This study aims to evaluate potential DDI and individualized therapy of clozapine in patients with depression based on real-world data.

Methods

Patient Information

We collected retrospective data related to patients with depression from Xuzhou Oriental Hospital Affiliated to Xuzhou Medical University between September 2020 and February 2025. This research was approved by the Research Ethics Committee of 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 adheres to the tenets of the Declaration of Helsinki. The inclusion criteria were as follows: (1) patients with depression, (2) clozapine treatment, (3) therapeutic drug monitoring for clozapine. Patients with depression but missing clinical medical record data were excluded. The collected data included patient's clozapine concentration data, physiological and biochemical data, and drug combination data. The drugs used concurrently by the patient during the use of clozapine were analyzed as potential concomitant medications. The analytical technique used for the determination of clozapine was homogeneous enzyme immunoassay. The sample extraction times for plasma concentrations were before the next administration, which is the value of the trough concentration.

Modeling

We constructed a DDI evaluation model using the population pharmacokinetics (PPK) method with non-linear mixed effect modeling software (NONMEM, version 7, ICON Development Solutions, Ellicott City, MD, USA). Given trough concentration, we researched the absorption phase with a one-compartment model. The information provided by the trough concentration was insufficient and could not accurately determine the Ka value, which needed to be fixed. Pharmacokinetic parameters, CL/F, V/F, and Ka (fixed at 1.3/h[32,33]), were included.

Equation (i) represents individual variation:

$$F_i = TV(F) \times \exp(\eta_i) \tag{i}$$

F_i represents individual parameter; TV(F) represents typical individual parameter; and η_i represents symmetrical distribution.

Equations (ii)–(iv) represent random residual variations:

$$H_i = G_i + \varepsilon_1 \tag{ii}$$

$$H_i = G_i + G_i * \varepsilon_1 \tag{iii}$$

$$H_i = G_i + G_{i*}\varepsilon_1 + \varepsilon_2 \tag{iv}$$

H_i represents observed concentration; G_i represents individual predicted concentration; and ε_n represents symmetrical distribution.

Equation (v) represents the relationship between parameters and weight:

$$I_i = I_{std} \times (L_i / L_{std})^N \tag{v}$$

I_i represents i-th individual parameter; L_i represents i-th individual weight; L_{std} represents standard weight of 70 kg; and I_{std} represents typical individual parameter. N represents the allometric coefficient: 0.75,1 for CL/F and V/F, respectively.[34]

Equations (vi) and (vii) represent continuous or categorical covariate parameters, respectively:

$$O_i = TV(O) \times (P_i / P_m)^S \tag{vi}$$

Table 1 Demographic Data of Patients with Depression Patients Being Treated with Clozapine (n = 29)

Characteristic	Mean ± SD	Median (Range)
Gender (men/women)	12/17	/
Age (years)	39.16 ± 16.17	42.86 (14.61–61.73)
Weight (kg)	71.58 ± 12.68	75.00 (45.00–100.00)
Albumin (g/L)	40.64 ± 2.82	40.50 (31.80–47.90)
Globulin (g/L)	25.74 ± 2.89	26.10 (17.90–32.10)
Alanine transaminase (IU/L)	37.00 ± 28.08	29.00 (8.00–144.00)
Aspartate transaminase (IU/L)	25.82 ± 13.28	21.00 (11.00–67.00)
Creatinine (μmol/L)	66.85 ± 16.58	64.00 (38.00–106.00)
Urea (mmol/L)	4.75 ± 1.01	4.76 (3.19–7.52)
Total protein (g/L)	66.38 ± 5.07	66.80 (51.80–80.00)
Total cholesterol (mmol/L)	4.87 ± 1.25	4.52 (3.11–7.41)
Triglyceride (mmol/L)	2.03 ± 1.15	1.68 (0.53–5.15)
Direct bilirubin (μmol/L)	2.60 ± 1.35	2.20 (0.50–6.80)
Total bilibrubin (μmol/L)	8.54 ± 4.74	7.50 (3.40–26.30)
Hematocrit (%)	40.11 ± 3.56	39.90 (34.50–47.70)
Hemoglobin (g/L)	135.08 ± 13.13	131.00 (109–164.00)
Mean corpuscular hemoglobin (pg)	30.87 ± 1.99	30.60 (26.30–37.60)
Mean corpuscular hemoglobin concentration (g/L)	336.71 ± 13.16	336.00 (312.00–368.00)

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$$O_i = TV(O)\times(1+S\times P_i) \tag{vii}$$

O_i represents individual parameter; TV(O) represents typical individual parameter; S represents parameter to be estimated; P_i represents covariate of the i-th individual; and P_m represents population median for the covariate.

Constructing the covariate model involved two steps. The objective function value (OFV) decreased by more than 3.84 ($P<0.05$) and increased by more than 6.63 ($P<0.01$), and were deemed the inclusion and exclusion standards, respectively.

Model Evaluation

To evaluate the final clozapine PPK model in patients with depression, observations vs population predictions, observations vs individual predictions, conditional weighted residuals (WRESs) vs population predictions, conditional WRES vs time, observations/predictions vs time, density vs weighted residuals, quantilies of weighted residuals vs quantilies of normal, and visual predictive checks (VPCs) were used. In addition, bootstrapping was used to repeat random sampling with replacement data from the raw database, involving 1000 repetitions. The medians and 2.5–97.5 percentiles of the bootstrapping results were used for comparison with final model parameters.

Concentration Simulation

The research simulates two circumstances: (1) patients with depression not prescribed fluvoxamine maleate, and (2) patients with depression prescribed fluvoxamine maleate. Each circumstance accounted for 1000 virtual patients with depression, and simulated five weight groups (40 kg, 60 kg, 80 kg, 100 kg, 120 kg) and ten dosage groups (1 mg/kg/day, 2 mg/kg/day, 3 mg/kg/

Table 2 Drug Combinations in Patients with Depression Being Treated with Clozapine (n = 29)

Drug	Category	N	Drug	Category	N
Alprazolam tablet	0	28	Nifedipine controlled-release tablet	0	28
	1	1		1	1
Diazepam injection	0	24	Paroxetine hydrochloride tablet	0	24
	1	5		1	5
Enteric-coated aspirin tablet	0	28	Phenhyxol hydrochloride tablet	0	25
	1	1		1	4
Escitalopram oxalate tablet	0	28	Propranolol hydrochloride tablet	0	23
	1	1		1	6
Fluvoxamine maleate tablet	0	25	Risperidone tablet	0	24
	1	4		1	5
Gabapentin capsule	0	27	Rosuvastatin calcium tablet	0	28
	1	2		1	1
Metformin hydrochloride tablet	0	28	Venlafaxine hydrochloride sustained-release capsule	0	25
	1	1		1	4
Metoprolol succinate extended-release tablet	0	27	Zaleplon Dispersible tablet	0	28
	1	2		1	1
Metoprolol tartrate tablet	0	28			
	1	1			

Notes: Category, 0: without drug, 1: with drug; N: number of patients.

day, 4 mg/kg/day, 5 mg/kg/day, 6 mg/kg/day, 7 mg/kg/day, 8 mg/kg/day, 9 mg/kg/day, 10 mg/kg/day). The scope of treatment was 350–800 ng/mL, and the toxicity threshold was 1000 ng/mL for clozapine.[35–38]

Results

Patient Data

This research focused on 29 patients with depression using real-world data: 12 men and 17 women. Ages ranged from 14.61–61.73 years, and weight variedfrom 45.00–100.00 kg. Table 1 shows patients' demographic data, and Table 2 lists drug combinations prescribed for them.

Modeling Results

Equations (ix) and (x) are the modeling results of clozapine in patients with depression:

$$CL/F = 21.6 \times (\mathrm{weight}/70)^{0.75} \times (1 - 0.565 \times \ \mathrm{FLU}) \tag{ix}$$

$$V/F = 140 \times (\mathrm{weight}/70) \tag{x}$$

FLU 1 represents patients receiving fluvoxamine maleate; FLU 0 represents patients not receiving fluvoxamine maleate.

Model Evaluation

Figures 1A–H are visual representations of the final clozapine PPK model. Figure 2 represents individual plots, and Table 3 represents bootstrap validation, showing that the clozapine PPK model of patients with depression is accurate and

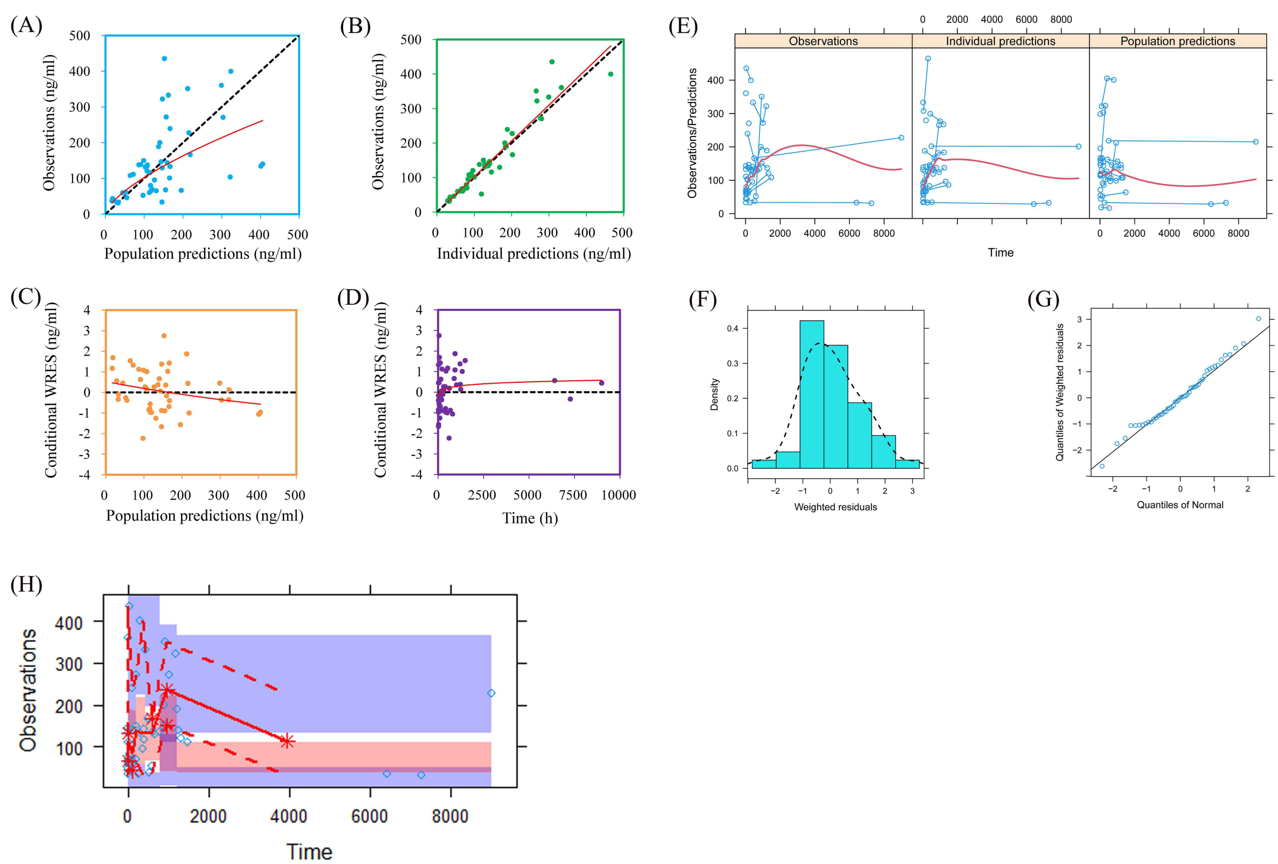

Figure 1 Visualized evaluation. (**A**) Observations vs population predictions. (**B**) Observations vs individual predictions. (**C**) Conditional weighted residuals (WRES) vs population predictions. (**D**) Conditional WRES vs time. (**E**) Observations/predictions vs time. (**F**) Density vs weighted residuals. (**G**) Quantilies of weighted residuals vs quantities of normal residuals. (**H**) Visual predictive check (VPC) of model. **P*<0.05.

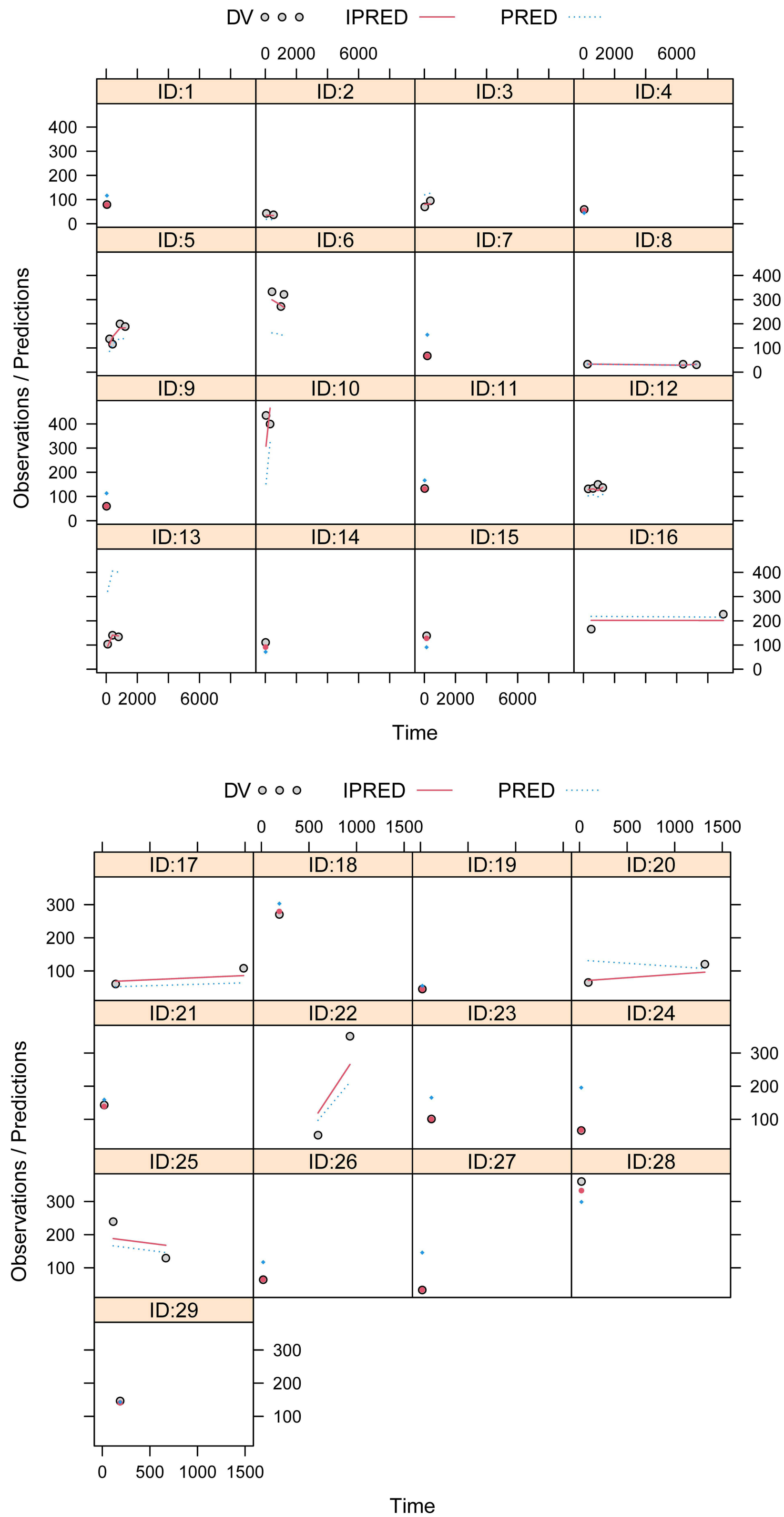

Figure 2 Individual plots.

Abbreviations: ID, patient ID number; DV, measured concentration value; IPRED, individual predictive value; PRED, population predictive value.

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

Parameter	Estimate	SE (%)	Bootstrap		Bias (%)
			Median	95% Confidence Interval	
CL/F (L/h)	21.6	11.0	21.5	[17.2, 35.9]	−0.46
V/F (L)	140	22.8	149	[90, 1060]	6.43
Ka (h^{-1})	1.3 (fixed)	–	–	–	–
θ_{FLU}	−0.565	9.6	−0.558	[−0.822, −0.397]	−1.24
$\omega_{CL/F}$	0.168	36.6	0.163	[0.047, 0.492]	−2.98
$\omega_{V/F}$	0.529	21.6	0.512	[0.015, 0.905]	−3.21
σ_1	0.218	19.9	0.205	[0.118, 0.385]	−5.96

Notes: 95% confidence interval was displayed as the 2.5th to 97.5th percentile of bootstrap estimates. CL/F, apparent oral clearance (L/h); V/F, apparent volume of distribution (L); Ka, absorption rate constant (h^{-1}); θ_{FLU} coefficient of fluvoxamine maleate; $\omega_{CL/F}$, inter-individual variability of CL/F; $\omega_{V/F}$, inter-individual variability of V/F; σ_1, residual variability, proportional error; Bias, prediction error, Bias = (Median-Estimate) /Estimate×100%.

reliable. Figure 3 represents the clozapine clearance rate of patients with depressio when they are treated with fluvoxamine maleate; it can decline by 56.5%.

Recommended Dosage

Figures 4A–E and 5A–E represent simulated clozapine concentrations of patients with depression who are and are not treated with fluvoxamine maleate. Figure 6 represents the probability of achieving the best results from clozapine treatment; Figure 6A shows the results of patients not being treated with fluvoxamine maleate; and Figure 6B shows the results of patients being treated with fluvoxamine maleate. Optimal dose selection is mainly based on a certain simulated dose within a specific weight range that has the highest probability of achieving the target. Five weight groups and ten dosage groups are simulated. Furthermore, 9 mg/kg, 8 mg/kg, 7 mg/kg, and 6 mg/kg of clozapine are recommended for people with depression weighing 40–47 kg, 47–70 kg, 70–100 kg, 100–120 kg, respectively, who are not being treated with fluvoxamine maleate; 3 mg/kg and 2 mg/kg are recommended for those weighing 40–70 kg and 70–120 kg, respectively, who are being treated with fluvoxamine maleate, as shown in Table 4. In addition, the probability of exceeding the upper limits of the safe dosage of clozapine are shown in Figures 7A and B for patients with depression

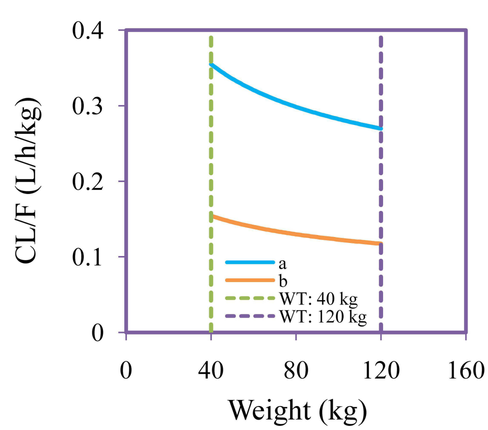

Figure 3 Clozapine clearance rate of patients with depression. a, Patients with depression not treated with fluvoxamine maleate. b, Patients with depression treated with fluvoxamine maleate.

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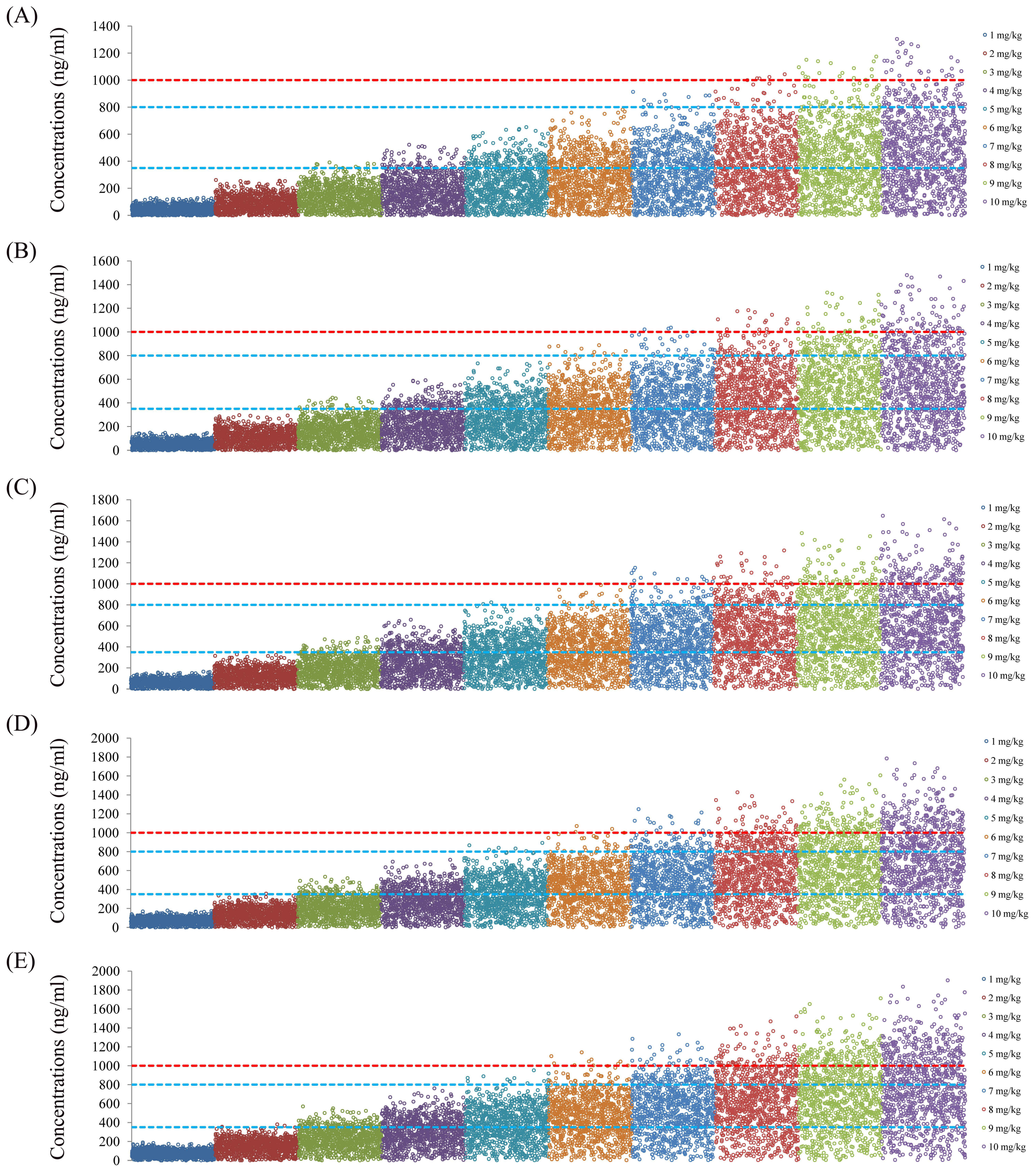

Figure 4 Simulated clozapine concentrations of patients with depression not treated with fluvoxamine maleate. (**A**) Patients weighing 40 kg. (**B**) Patients weighing 60 kg. (**C**) Patients weighing 80 kg. (**D**) Patients weighing 100 kg. (**E**) Patients weighing 120 kg.

who are and are not being treated with fluvoxamine maleate. For patients not taking fluvoxamine maleate, the probability of exceeding the upper limit of the safe dosage is less than 2.6%. For those taking fluvoxamine maleate, the probability of exceeding the upper limit is less than 2%. The safety information is also shown in Table 4.

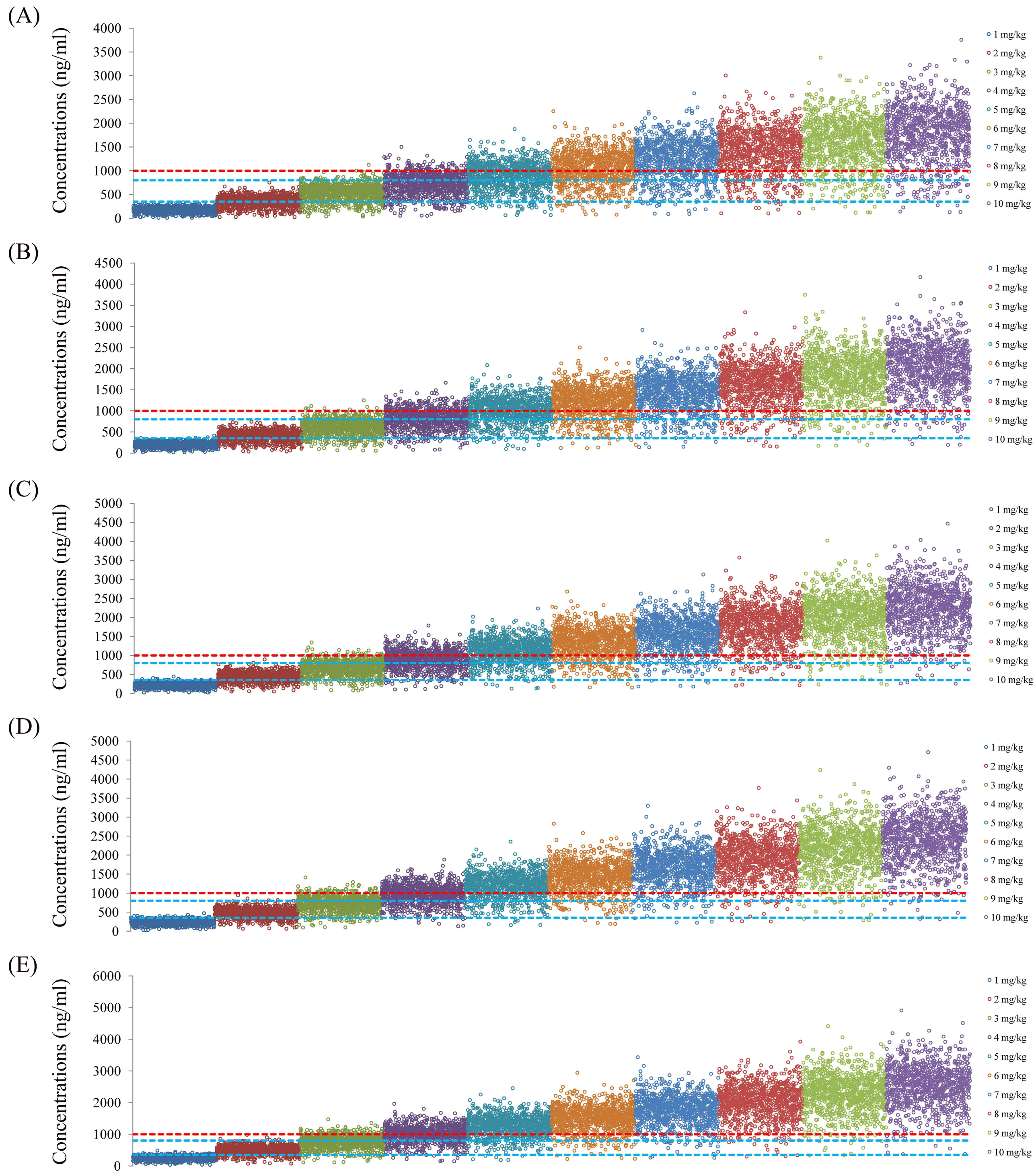

Figure 5 Simulated clozapine concentrations of patients with depression being treated with fluvoxamine maleate. (**A**) Patients weighing 40 kg. (**B**) Patients weighing 60 kg. (**C**) Patients weighing 80 kg. (**D**) Patients weighing 100 kg. (**E**) Patients weighing 120 kg.

Discussion

Clozapine is a type of antipsychotic, specifically used in the treatment of refractory schizophrenia. When other similar drugs fail to relieve symptoms such as auditory hallucinations and delusions, it can effectively control the condition and reduce the risk of self-harm for patients. Clozapine's main mechanism of action is to regulate neurotransmitters in the brain.[39–41] In patients with depression, clozapine cannot replace conventional antidepressants and is only used as

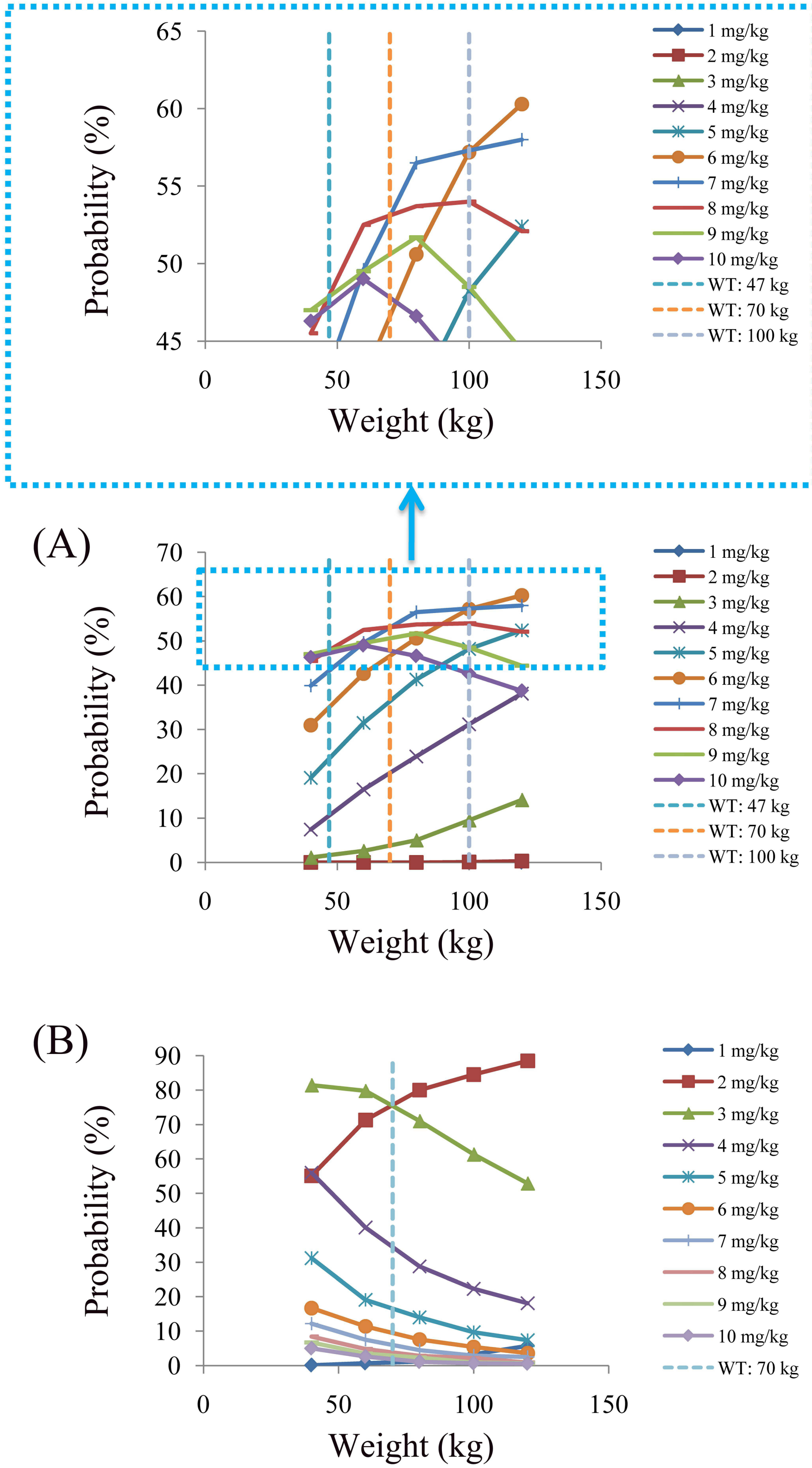

Figure 6 Probability of achieving the scope of clozapine treatment in patients with depression patients. (**A**) Patients not being treated with fluvoxamine maleate. (**B**) Patients being treated with fluvoxamine maleate.

Table 4 Initial Clozapine Dosage Recommendations for Patients with Depression

Without Fluvoxamine Maleate			With Fluvoxamine Maleate		
Body Weight (kg)	**Dosage (mg/kg/day)**	**Probability of Exceeding the Upper Safe Dosage Limit (%)**	**Body Weight (kg)**	**Dosage (mg/kg/day)**	**Probability of Exceeding the Upper Safe Dosage Limit (%)**
[40–47)	9	< 2.6	[40–70)	3	< 2
[47–70)	8	< 2.3	[70–120]	2	0
[70–100)	7	< 1.9			
[100–120]	6	< 1			

a second-line or combination medication. Clozapine can alleviate psychotic symptoms and improve the depressive state only when patients with severe depression experience delusions (such as self-guilt delusions) or hallucinations (such as negative auditory hallucinations) consistent with the depressive mood.[18–26]

Serious adverse reactions of clozapine include agranulocytosis, myocarditis and myocardial injury, epileptic seizures, hypothyroidism, macular degeneration, and gastrointestinal problems. Most of these adverse reactions are significantly related to the concentration of clozapine.[42–50] Clinically, the next dosage of clozapine is often adjusted based on feedback from therapeutic drug monitoring (TDM) results.[51–53] However, when used in patients with depression, it is not clear whether the combined use of multiple drugs will affect the drug concentration level of clozapine and thereby affect its dosage.

This research involved 29 patients with depression from the real world, utilizing their clozapine concentration data, physiological and biochemical data, and drug combination data to construct a DDI evaluation model using the population pharmacokinetics (PPK) method. PPK is a branch of pharmacokinetics that studies the metabolic patterns, parameter distribution characteristics and influencing factors of drugs in a specific population by integrating classical pharmacokinetic principles with statistical methods. The core objectives include quantifying inter-individual/intra-individual variations, identifying key covariates, particularly DDI, and optimizing individualized dosage regimens.[54,55]

Regarding the issue of the number of patients in this study, it is similar to that of many published articles. For example, in Bayoumy et al's study, population pharmacokinetics model of thioguanine in patients with inflammatory bowel disease, the sample size is 28.[56] In Baklouti et al's study on ceftobiprole use in critically ill patients and their proposal for new dosage regimens, the sample size is 27.[57] In Vonk et al's study on the real-world pharmacokinetics of elexacaftor-tezacaftor-ivacaftor in children with cystic fibrosis, a prospective observational study, the sample size is 29.[58] In Schoenmakers et al's study on the pharmacokinetics of betamethasone in pre-eclampsia, an in vivo and ex vivo study, the sample size is 28.[59] Based on this data, although the number of patients in this study is not very large, it is still sufficient.

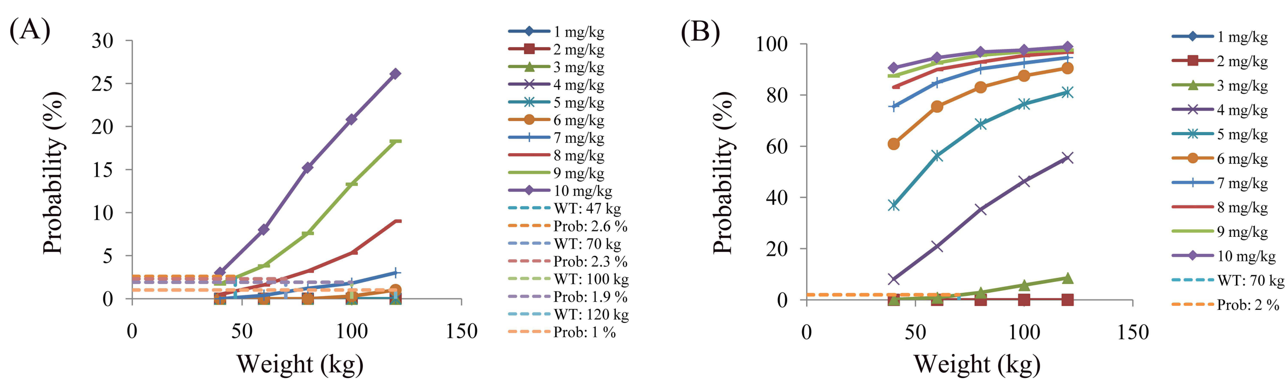

Figure 7 Probability to exceed the upper limit of the clozapine safe concentration in depression patients. (**A**) Depression patients without fluvoxamine maleate. (**B**) Depression patients with fluvoxamine maleate.

At present, using PPK modeling to analyze DDI has become a regular practice. Zhang et al report the DDI of paroxetine on olanzapine and initial dosage optimization in patients with major depressive disorder based on PPK.[10] Saqr et al report steroid–tacrolimus DDI and the effect of CYP3A genotypes.[60] Zhang et al report the effects of aripiprazole on olanzapine PPK and initial dosage optimization in schizophrenia patients.[61] Ngo et al report application of the PPK model-based approach to the prediction of DDI between rivaroxaban and carbamazepine in humans.[62] Chow et al report the utility of PPK modeling in the assessment of therapeutic protein-drug interactions.[63] Xin et al report PPK analysis from Phase I and Phase II studies of the humanized monovalent antibody, onartuzumab, in patients with advanced solid tumors.[64]

This study analyzes potential DDI drugs through PPK modeling, including alprazolam tablets, diazepam injections, enteric-coated aspirin tablets, escitalopram oxalate tablets, fluvoxamine maleate tablets, gabapentin capsules, metformin hydrochloride tablets, metoprolol succinate extended-release tablets, metoprolol tartrate tablets, nifedipine controlled-release tablets, paroxetine hydrochloride tablets, phenhyxol hydrochloride tablets, propranolol hydrochloride tablets, risperidone tablets, rosuvastatin calcium tablets, venlafaxine hydrochloride sustained-release capsules, and zaleplon dispersible tablets. The results of our research reveal that fluvoxamine maleate has a noteworthy DDI with clozapine, and can reduce the clearance rate of clozapine in patients with depression by 56.5%. This phenomenon can be explained from the perspective of pharmacological mechanisms: clozapine is mainly metabolized by CYP1A2 and CYP3A4, and fluvoxamine is a strong inhibitor of CYP1A2 (the primary metabolic pathway for clozapine).

In terms of dosage, 9 mg/kg, 8 mg/kg, 7 mg/kg, and 6 mg/kg clozapine are recommended for patients with depression weighing 40–47 kg, 47–70 kg, 70–100 kg, and 100–120 kg, respectively, who are not taking fluvoxamine maleate; 3 mg/kg and 2 mg/kg clozapine are recommended for those weighing 40–70 kg and 70–120 kg, respectively, who are taking fluvoxamine maleate. In addition, in terms of safety, we find that for patients with depression who are not taking fluvoxamine maleate, the probability of exceeding the upper limit of the safe dosage is less than 2.6%. For patients taking fluvoxamine maleate, the probability of exceeding the upper limit of the safe dosage is less than 2%. Therefore, the dosage of clozapine for patients with depression that we recommend has a relatively high level of safety.

Of course, this study also has certain limitations. This study is based on a single-center retrospective study using PPK to predict the DDI of clozapine in patients with depression, and its small sample size, single-center nature, and retrospective design are issues to be considered. In terms of clinical application, the main focus of this study was Chinese patients with depression. In future, prospective multicenter and multinational studies are needed to further verify our conclusions. In addition, polymorphisms might be related to inter-individual variations in clozapine and this information is not included in the present dataset. However, the clozapine PPK model with genetic polymorphisms might not be practical for simulating drug dosage data from TDM in the real world because, at present, no routine genetic testing has been conducted in patients treated with clozapine and genetic data is often missing. Dialectically speaking, our model in the present study may have better clinical and practical value in the real world and thus requires more external validation. Of course, this study does not take into account the influence of lifestyle factors such as smoking and coffee consumption, which need to improve in the future.

Conclusion

Our research evaluated potential DDI and individualized clozapine therapy in patients with depression based on real-world data, providing a basis for its individualized administration. When a patient with depression patient is treated with fluvoxamine maleate, the dosage of clozapine needs to be reduced.

Data Sharing Statement

The de-identified participant data and codes 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.

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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