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ORIGINAL RESEARCH

External Validation of the Population Pharmacokinetic Models of Amisulpride and Remedial Strategies for Delayed or Missed Doses

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Objective: This study aimed to evaluate the predictive performance of published amisulpride population pharmacokinetic (PopPK) models in schizophrenia patients with an external data set and establish remedial dosing regimens for nonadherent amisulpride-treated patients.

Methods: A systematic search was conducted on PubMed, Embase, and Web of Science to identify PopPK models for evaluation. The evaluation process involved analyzing 390 serum concentration samples obtained from 361 Chinese adult inpatients diagnosed with schizophrenia. Model predictability was evaluated by prediction-based and simulation-based diagnostics. Based on validation results, a modified PopPK model was constructed to characterize amisulpride pharmacokinetic in our patients. Monte Carlo simulation was employed to investigate non-adherence scenarios and the impact of subsequently administered remedial regimens.

Results: In the five assessed published models, four included trough concentrations from schizophrenia patients, and one combined single-dose data from healthy older adults and trough concentrations from older adults with Alzheimer's disease. The PE for population and individual predictions ranged from −92.89% to 27.02% and −24.82% to 4.04%, respectively. In the simulation-based diagnostics, the NPDE results indicated noticeable bias in all models. Therefore, a modified one-compartment model, with estimated creatinine clearance(eCLcr) as covariates on the apparent clearance (CL/F) of amisulpride, was developed. For delays in medication dosing, if the delay is within 12 hours, take half the missed dose right away, then resume the normal schedule; if the delay is up to 24 hours, just continue with the regular dosing schedule.

Conclusion: Existing published models lack the necessary reliability for cross-center application. Future prospective studies are required to assess our model before integrating it into clinical practice. Model-based simulations provided a rational approach to propose remedial strategies for delayed or missed doses.

Keywords: population pharmacokinetics, amisulpride, schizophrenia, external validation, adherence

Introduction

Amisulpride, an atypical antipsychotic that acts on D2, D3, and 5-HT7 receptors, is highly regarded for its substantial clinical efficacy, particularly in addressing cognitive and emotional symptoms while minimizing metabolic side effects.[1] Remarkably, it demonstrates clinical effectiveness in treating both positive and negative symptoms, as well as acute and chronic forms of schizophrenia.[2] Amisulpride is quickly absorbed and exhibits a biphasic absorption profile, with peak plasma concentration occurring around 1.5 hours post-dosing, followed by a secondary peak between 3 and 4 hours. Its bioavailability is approximately 48% due to reduced first-pass metabolism.[3,4] Amisulpride has low affinity for plasma protein binding.[3,5] Within 24 hours, 90% of amisulpride is excreted through the kidneys, and with repeated dosing, there is no accumulation in the body.[5] Concurrently, amisulpride serves as a substrate for SLC22 family organic ion transporters in the kidneys,[6] and the renal excretion rate is roughly 2.5 times greater than what glomerular filtration would expect,[7,8] indicating that active renal secretion is likely the predominant elimination pathway.

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Elevated inter-individual variability (IIV) of amisulpride has been observed in patients and is considered the primary recommendation for the utilization of therapeutic drug monitoring (TDM).[7,9] This variability could be explained by various factors, including age, weight, and renal function.[10–14] In contrast to conventional pharmacokinetic approaches, PopPK offers an advantageous means of analyzing sparse TDM data, enabling the estimation of both intra- and interindividual variabilities, as well as the prediction of optimal starting doses without the need for actual concentration measurements.[15]

While numerous studies have documented PopPK models for amisulpride;[10–14] however, these studies were confined to single-center settings and did not undergo a comprehensive evaluation of their predictive capacity. As such, it remains uncertain if the findings from these investigations are universally applicable across different clinical centers. Of particular significance is the fact that amisulpride exhibits substantial inter- and intra-individual pharmacokinetic variability, which underscores the importance of employing external datasets to conduct a thorough appraisal of the published PopPK models specific to amisulpride use in schizophrenia patient.[16] This step would serve to validate and broaden the applicability of these models across diverse clinical scenarios.

Adherence to antipsychotic medication is crucial for symptom improvement and reducing relapse rates.[17] Studies have indicated that medication non-adherence among individuals with schizophrenia can range from 56% to 60%, with relapse rates ranging from 75% to 90%.[18,19] Many individuals with schizophrenia may experience non-adherence to their medication at some point during their treatment, putting them at a significantly elevated risk of illness exacerbation, relapse, and re-hospitalization.[20] Recent studies propose that enhancing medication adherence could have a more significant influence on overall health outcomes compared to specific medical interventions.[21] However, there are little evidence to support the non-adherence scenarios remedy, therefor, further research is essential to investigate strategies for promoting adherence and reducing the negative effects of non-adherence.

The primary objective of this study was to perform an external validation of the existing amisulpride PopPK models in an independent patient cohort. If external validation showed that the amisulpride model did not fully capture amisulpride PK in the cohort, a secondary objective was to develop a modified PopPK model for improving the current amisulpride TDM. Moreover, a model-based simulation will be conducted to assess the effect of missed or delayed doses on the pharmacokinetics of amisulpride, propose the practical recommendations.

Methods

Literature Search

A thorough literature search was conducted to gather data on PopPK models of amisulpride. Databases such as PubMed, Web of Science, and Embase were scrutinized, encompassing publications up until September 2023. The search strategy used the following terms: ("amisulpride" OR "dan 2163" OR "4 – amino – n - ((1 - ethyl-2- pyrrolidinyl)methyl) – 5 - (ethylsulfonyl) – 2 - methoxybenzamide"OR "solian") AND ("population pharmacokinetic" OR "pharmacokinetic modeling" OR "NONMEM" OR "nonlinear mixed effects model" OR "WINNONMIX") The reference lists of the identified publications were also screened to identify other potential publications for inclusion. Inclusion criteria consisted of the following: 1) Study drug: amisulpride, 2) Publication in English, and 3) PopPK studies conducted using nonlinear mixed-effects modeling methods. Exclusion criteria include: 1) Duplicate articles; 2) Insufficient details for external evaluation; 3) Publications categorized as reviews or methodological articles; and 4) non-parametric model. The following information was extracted from the original studies: structure of the compartmental model, PopPK parameters, covariate model, inter- and intra-individual variability, residual variability, and estimation method.

Data Accumulation and Blood Sampling

A retrospective analysis was conducted, gathering TDM data from 361 inpatient diagnosed with schizophrenia and treated with amisulpride at the Xi'an Mental Health Center between 2017 and 2021. Among these patients, 302 individuals received twice-daily dosing, while 59 individuals received once-daily dosing. Inclusion criteria stipulated that patients must have received oral amisulpride for a minimum of 72 hours under serum drug concentration monitoring.[22] Clinical information and patient demographics were extracted from hospital medical records. This included the time of blood sampling, daily dose, duration of amisulpride treatment, drug concentrations, weight, age, gender, concomitant medications, information regarding renal and hepatic function (as uric acid, blood urea nitrogen, creatinine, total protein, and albumin), the eCLcr calculated using the Cockcroft-Gault formula and the estimated glomerular filtration rate (eGFR) calculated using the CKD-EPI formula.[23,24]

After patients have taken a stable dose of amisulpride for at least five half-lives (when plasma levels have reached a steady state), blood samples were collected at 6:00 AM, prior to the next dose.[25,26] The steady-state plasma concentrations of amisulpride were measured using a validated liquid chromatography-tandem mass spectrometry 8050 (LC-MS/MS) system (Shimadzu Corporation in Kyoto, Japan). The linear range for amisulpride quantification spanned from 20 to 2000 $ng \cdot mL^{-1}$, with relative intra- and inter-day precisions expressed as standard deviation (RSD) falling within 5%. Moreover, the recovery rates ranged from 80% to 120%, indicating good stability.

Model Evaluation

The published models were reconstructed by extracting formulas and parameters from each identified article. Based on the PopPK model using maximum posterior Bayesian estimation (MAP-BE), combined with dose, sampling time, and covariates recorded in the validation dataset, the predicted concentration was generated. By employing the PK parameters reported in the model, the predicted population and individual concentrations were calculated at the same sampling time as our own data. In cases where the covariates specified in the PopPK model were not available in the evaluation dataset, the mean or median values of the covariates described in the original publication were utilized.

Prediction-Based Diagnostics

The predictive performance of the model was assessed using both visual and quantitative methods. Goodness-of-fit plots (GOF) graphs are used to evaluate the predictive performance. A visual assessment was conducted by comparing the observed concentration (Cobs) with both the overall predicted concentration (Cpred) and the individual predicted concentration (Cipred).

To evaluate the accuracy and precision of the predicted concentrations, the population predicted concentrations were estimated and compared to the corresponding observed value. The prediction error (PE%) for each individual, the mean prediction error (MPE%), and the relative root mean squared error (RMSE%) were calculated. Here, N represents the number of amisulpride observations, while $\boldsymbol{C_{i,pred}}$ and $\boldsymbol{C_{obs}}$ denote the predicted and observed concentrations for a given patient, respectively.[27]

$$PE = \frac{C_{i,pred} - C_{obs}}{C_{obs}}$$

$$MPE = \frac{1}{N}\sum_{i=1}^{N} PE$$

$$RMSE = \sqrt{\frac{1}{N}\sum_{i=1}^{N} PE^2}$$

Simulation-Based Diagnostics

The predictive performance of candidate models was assessed using prediction-corrected visual predictive checks (pcVPC). A total of 1000 simulations were conducted on the concentration distribution, and these simulated values were compared with observed data to evaluate the predictive accuracy of the models. pcVPC facilitates a visual examination of the consistency in the concentration-time profiles of amisulpride across the 5th percentile, median, and 95th percentile over time.

A predictive performance at the population level was assessed by means of simulation using normalized prediction distribution error (NPDE). NPDE was computed for the validation set based on 1000 simulations from the final model using the NPDE package (version 2.0). In order to compare the distribution of NPDE values with the reference distribution, graphical

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methods and appropriate statistical tests were employed. Three statistical tests were utilized, namely the Wilcoxon signed-rank test (H0: mean = 0), the Fisher variance test (H0: variance = 1), and the Shapiro–Wilks test (H0: normal distribution).

PopPK Model Development and Validation

The PopPK model of amisulpride was developed using the nonlinear mixed effects modeling (NONMEM® version 7.4.0 ICON Development Solutions, Ellicott City, MD, USA) method. One- and two- compartment models were compared for analyzing the amisulpride plasma concentrations. A first-order conditional estimation with interaction (FOCE-I) was used to estimate the parameters. The modified model optimization primarily relies on models with good predictive performance. The dataset predominantly consists of trough concentration data following long-term administration, making it challenging to accurately estimate the drug absorption process. Based on articles with favorable predictive performance, taking into account the racial similarity among the Chinese population, which the absorption rate constant (Ka) is fixed at 0.18.[7,13] The model parameters presumably followed log-normal distributions and IIV was incorporated for individual structural variables. The IIV was determined using the exponential model:

$$P_i = P_{TV} \times \mathrm{Exp}\,(\eta_i)$$

whereby P_i represented the *i*th individual parameter, P_{TV} was a typical parameter population value, and η_i was a random variable with a zero average and ω^2 variance.

Test residuals using additive, proportional, and combined error structures, as follows:

Additive error model: $C_{obs} = C_{pred} + \varepsilon_{add}$

Proportional error model: $C_{obs} = C_{pred} \times (1+\varepsilon_{prop})$

Mixed error model: $C_{obs} = C_{pred} \times (1+\varepsilon_{prop}) + \varepsilon_{add}$

Here, C_{obs} represented the actual circulating amisulpride levels, and C_{pred} was the matched model estimated amisulpride value, ε_{add} and ε_{prop} were random error that conformed to a normal distribution with a zero average and σ variance.

The covariates were screened using a series of forward inclusion and backward exclusion.[28] A covariate inclusion enhanced the model fit, leading to a reduction in the objective functional value (OFV). Using forward inclusion, the covariates were included in the model when the OFV reduction exceeded 6.64 ($P < 0.01$). For the backward exclusion step, a covariate was retained in the final model if the associated OFV increase exceeded 10.83 ($P < 0.001$). The Akaike's Information Criterion (AIC) was calculated to strike a balance between model fit and complexity, with smaller AIC values indicating a better fit of the new model to the data.

The final model was further assessed with GOF, the bootstrap and VPC. A total of 1000 bootstrap datasets were generated by resampling the original dataset. The final-model parameter predictions were then analyzed based on the medians and 95% confidence intervals (CIs) derived from the bootstrap estimations. The absence of any significant differences indicated the reliability of the final model.[29]

Nonadherence Scenarios and Remedial Strategies

For clinical feasibility, it is advised that if a dose is delayed or missed, patients should take the remedial dose regimen at two time points, including the time when they remembered the delayed dose and the time for the next scheduled dose.[30,31] Therefore, upon the occurrence of a delayed or missed dose, an exploration into the subsequent remedial strategies was undertaken:

Strategy A administer the regular dose immediately and then a regular dose as the next scheduled time.

Strategy B administer a partial dose immediately and then a regular dose as the next scheduled time.

Strategy C administer the regular dose immediately and then a partial dose as the next scheduled time.

Strategy D administer both partial and regular doses immediately; the next scheduled time is skipped, and then resume the regular dosing regimen.

Strategy E administer both partial and regular doses immediately, and then resume the regular dosing regimen.

Strategy F administer 2-fold regular doses immediately, and then resume the regular dosing regimen.

The individual therapeutic range, which is defined as the concentration interval spanning from the 5th percentile trough concentration to the 95th percentile peak concentration at the steady state of a given dose, represents the optimal response in an individual patient for each treatment regimen. The percentage of time within the therapeutic range was utilized as a key indicator for evaluating the effectiveness of remedial strategies.

Results

Datasets Profiles

The patient demographics and other covariates are listed in Table 1. A total of 390 observations were collected from 361 subjects. The mean age was 32 years with a range of 18 to 67 years. The mean weight was 62kg with a range of 40 to 109kg. The plasma concentrations of amisulpride ranged from 54.7 to 1955.7 ng/mL, with a daily dosage range of 200–2000 mg (median = 600 mg).

Literature Search and Summary of Published PopPK Models

The literature search identified a total of five studies detailing the PopPK of amisulpride. Five PopPK models (named M1-M5, respectively) of amisulpride were included for the external evaluation.[10–14] The demographics, clinical characteristics, and doses for the patients of the included studies are summarized in Table 2. Among the evaluated models, three were based on data from patients in China,[10,13,14] while the remaining models were developed for patients in France, the UK,[11] and Swiss.[12]

The key information of the included PopPK models were presented in Table 3. The disposition of amisulpride was characterized by a one-compartment model in four studies and a two-compartment model in one study.[11] Typical estimates for amisulpride clearance in the included studies ranged from 32.6 to 61.1 L/h. In studies utilizing a one-compartment model, the distribution volume varied ranging from 391 to 1720.[10,13] All models accounted for the IIV associated with clearance, with values ranging from 3.03% to 36.0%.[10,11] The above studies found that several covariates significantly impact the pharmacokinetics of amisulpride. The most common covariates affecting the CL/F include age, weight, eCLcr, and eGFR. Regarding residual unexplained variability, various forms were applied, including additive (including the additive error on the natural log-transformed concentrations), proportional, or combined proportional and additive error models.

Model Evaluation

The covariate “lean body mass” in Model M3 was not collected in our dataset, so it was fixed at the median value of 52 from the original Model M3 study for model evaluation purposes. The GOF plots (observed concentration (DV) versus

Table 1 Characteristics of External Evaluation Dataset

Characteristics	Median (range)	Number or mean ± SD
No. of patients (Male/Female)	361(150/211)	/
No. of samples	390	/
Age (years)	32(18,67)	34.42±10.56
Body weight (kg)	62(40,109)	62.93±11.71
daily dose(mg)	600(200,1200)	555.90±192.56
Amisulpride concentration (ng/mL)	471.8(54.7,1955.7)	546.03±341.76
Dose-corrected concentration (ng/mL/mg)	0.88(0.17,3.26)	0.970±0.474
UA (μmol/L)	297(81,698.9)	305.03±89.86
Urea (mmol/L)	3.5(0.6,10.1)	3.72±1.37
CR(μmol/L)	60(30,148.9)	66.34±15.7
eCLcr (mL/min)	114.42(23.29,239.51)	116.7±33.53
eGFR	118.5(79.9,146.5)	117.7±10.4
TP(g/L)	67(50,95.3)	67.56±6.83
ALB(g/L)	40(30,64)	40.8±4.7

Abbreviations: UA, uric acid; Cr, creatinine; eCLcr, estimated creatinine clearance; calculated using the Cockcroft-Gault formula; eGFR, estimated glomerular filtration rate; calculated using the CKD-EPI equation without the race component; TP, Total Protein; ALB, albumin; SD, standard deviation.

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Table 2 Characteristics of Included Population Pharmacokinetic Studies

Study (Publication Year)	Type of Study	Country	Subjects	No. of Subjects (M/F)	Age(year) Mean ±SD Median [Range]	Weight(Kg) Mean ±SD Median [Range]	Creatinine (μmol/l) Mean±SD Median [Range]
M1 Wei L. (2023)[10]	Retrospective	China	Psychiatric inpatients	88(69/19)	35.23 ± 10.7	68.12 ± 13.9	75.77 ± 14.98
M2 Suzanne R. (2016)[11]	Open observational	France, UK	Healthy elderly participants, AD patients	Study1: 20 (10/10) Study2: 41 (25/16)	Study1:68.7 ± 4.1 Study2: 82 ± 6.6	Study1:66.6 ± 9.1 Study2: 68.0 ± 15.2	Study1:56 ± 10.2 Study2: 83.1 ± 25.7
M3 Anaïs G.(2019)[12]	Retrospective	Swiss	Schizophrenia or schizotypal disorders patients	242(132/110)	37 (18–91)*	75 (43–185)*	76 (44–167)*
M4 Shanqing H.(2021)[13]	Retrospective	China	Psychiatric inpatients	121(58/63)	35.83±13.50	62.73±12.86	65.05±16.61
M5 Anning L.(2023)[14]	Retrospective	China	schizophrenia patients	776(301/475)	33.0 (23.0,47.0)*	66.0 (57.0, 79.0)*	116 (95.3, 144)*
Study (Publication Year)	eCLcr (mL/min) Mean±SD Median [Range]	eGFR	No. of Observation	Sampling design	Dosage regimen Mean±SD Median [Range]	Bioassay [LOQ](ng/ L)	
M1 Wei L. (2023)[10]	114.30 ± 31.25	NR	168	Steady-state pre-dose blood samples (trough concentrations)	681.55mg ± 222.84	2D-LC–UV[12]	
M2 Suzanne R. (2016)[11]	Study1:80.5 ± 17.5 Study2:67.7 ± 17.3	NR	Study1:280 Study2:41	Study1:before and at 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 32, 48 and 72 h Study2: Steady state	Study1:50mg Study2: 49.4mg ± 11.2	study1:HPLC [0.5] study2:LC-MS/MS[9]	
M3 Anaïs G. (2019)[12]	93 (20–180)	NR	513	a median time of 13.3 h (range 0.05–58 h) after the last dose (trough concentrations)	600mg (50–2000)	HPLC-MS[1]	
M4 Shanqing H. (2021)[13]	NR	NR	330	Steady state (trough concentrations)	NA	HPLC-MS[NR]	
M5 Anning L. (2023)[14]	NR	114 (101, 130)*	2328	Trough concentrations	566mg±264	UPLC-MS/MS[0.01]	

Note: *Median (IQR).

Abbreviations: M, male; F, female; SD, standard deviation; AD, Alzheimer's disease; eGFR, estimated glomerular filtration rate; eCLcr, estimated creatinine clearance; 2D-LC–UV, two-dimensional liquid chromatography with ultraviolet detection method; HPLC, high-performance liquid; LC-MS/MS, liquid chromatograph mass spectrometer or mass spectrometer; HPLC-MS, high-performance liquid chromatography mass spectrometry; UPLC-MS/MS, ultra-performance liquid chromatography tandem mass spectrometry; LOQ, lower limits of quantification; NR, not reported.

Table 3 Modelling Strategies and Final Pharmacokinetic Parameters of Included Studies

Study (Publication Year)	**Software/ Algorithm**	**Structural Model**		**Fixed Effect Parameters**	
M1 Wei L. (2023)[10]	NONMEM (FOCE-I)	1 CMT with FO absorption and elimination	CL/F (L/h) = V/F (L) = Ka (h^{-1})=	$32.6\times (eCLcr / 114.3)^{0.485}$ 391 0.9 (fixed)	
M2 Suzanne R. (2016)[11]	Monolix(NLME)	2 CMT with NA	Cl_i= V1= Q= V2= Ka=	$54.3\times (age_i/76)^{-2.9} \times (weight_i/70)^{0.75}$ 455 111 736 0.85	
M3 Anaïs G. (2019)[12]	NONMEM +PsN - Toolkit (NLME)	1 CMT with FO absorption and elimination	CL (L/h)= V (L)= Ka (h^{-1})=	43.9 × (1–0.47 × ((age - 37)/37)) × (1 + 0.53 × ((lean body weight – 52)/52) 926 0.9 fixed	
M4 Shanqing H. (2021)[13]	NONMEM (FOCE-I)	1 CMT with FO absorption and elimination	CL/F = V/F= Ka =	$1.04\times (AGE/32)^{-0.624}$ 1720 0.18	
M5 Anning L. (2023)[14]	NONMEM (FOCE-I)	1 CMT with linear elimination	CL/F = V/F= Ka =	$60.5\times (eGFR/113.87)^{0.817}$ 645 0.106	
Study (Publication Year)	Interindividual Variability	Residual Variability	Internal Validation	External Validation (N=number of samples)	Model Application
M1 Wei L. (2023)[10]	3.03%	prop:4.87%	GOF bootstrap NPDE	NR	NR
M2 Suzanne R. (2016)[11]	36% 43% 63% 46% 48%	σ (group 1): prop: 13% σ (group 2): prop: 53%	VPC	NR	Dose recommendation s based on amisulpride trough concentrations
M3 Anaïs G. (2019)[12]	34% 58% /	prop: 53%	VPC bootstrap	NR	Dose recommendations based on amisulpride trough concentrations
M4 Shanqing H. (2021)[13]	30.10% 122.50% /	prop: 6.4%	GOF bootstrap NPDE	NR	Dose recommendations based on amisulpride trough concentrations
M5 Anning L. (2023)[14]	35.90% 130.90% /	prop: 34.6%	GOF bootstrap NPDE	N = 145	Dose recommendations based on amisulpride trough concentrations

Abbreviations: CL, apparent clearance (L/h); Q, the intercompartment clearance; V, apparent volume of distribution (L); Ka, absorption rate (h^{-1}); eCLcr, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; NONMEM, nonlinear mixed effects modeling; FOCE, first order conditional estimation; FOCE-I, FOCE with the interation; CMT, compartment; FO, first-order; NLME, Nonlinear mixed effects modelling; PSN, Perl-speaks-NONMEM; GOF, goodness-of-fit plot; VPC, visual predictive check; NPDE, normalized prediction distribution errors; prop, Proportional residual error; NR, not reported.

individual predicted concentrations (IPRED) and DV versus population-predicted concentration (PRED)) in Supplementary Figure S1 represent the overall accuracy (bias) and precision of the model. In terms of population predictions, the model proposed by Model M2[11] displayed a notable underestimate when compared to the observed results, whereas the model proposed by Model M5[14] displayed a notable overestimation. Regarding individual predictions, the model proposed by Model M2[11] and M4[13] exhibited a tendency to underestimate the predictions when compared to the observed results, whereas the model proposed by Model M3[12] displayed a notable underestimate.

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Meanwhile, the model proposed by Model M1[10] demonstrates good predictive performance in both individual and population predictions.

The diagnostic results based on predictions are depicted in Supplementary Figure S2 and summarized in Table 4. Models M1[10] and M5,[14] with Median PE ≤ 30%, MPE ≤ 20%, and RMSE ≤ 20%, outperform the other models. Furthermore, Model M1,[10] characterized by Median PE ≤ 10%, MPE ≤ 10%, and RMSE ≤ 10%, exhibits the highest accuracy and precision, indicating a relatively satisfactory prediction performance. In individual predictions, only Model M3[12] displays a distribution of Median PE exceeding ±20%, while all other models demonstrate acceptable levels of bias. In population predictions, Models M2[11] and M4[13] exhibit Median PE distributions beyond ±20%, rendering them the models with the largest biases among those evaluated. Regarding the MPE and RMSE, all models display acceptable levels of deviation.[10–14]

The simulation-based diagnostics data is presented in Supplementary Figure S3. Quantile-quantile plots and NPDE histograms for all models reveal a non-normal distribution. Additionally, there is evident bias in NPDE regarding temporal changes or predicted concentrations. In terms of the global test, the corrected p-values for all models are <0.001, indicating that none of the models exhibited satisfactory performance in terms of prediction and diagnosis based on simulations.[10–14]

The results of the pcVPC experiment are illustrated in Supplementary Figure S4. The results of pcVPC shows a varying discrepancy between the observations and model simulations in all reported studies. A clear tendency of either over- or under-prediction was observed for all models.[10–14] The M5 showed relative superiority in the pcVPC plot.[14] Although there was a slight inconsistency between the 5th percentiles of the observed data and the simulated intervals of the corresponding percentiles, the 50th and 95th percentiles of the observed amisulpride concentrations were mostly situated within the associated CIs of the simulated data.

PopPK Model Development and Validation

The pharmacokinetics of amisulpride was most accurately described by a one-compartment model with first-order absorption and elimination. Upon integrating the combined medication information, it became evident that it could not be integrated as a covariate into the model due to significant differences between the groups. In this study, the demographic factors, laboratory indicators, and daily dosage were considered as covariates. Following forward inclusion and backward exclusion of covariates (Supplementary Table S1), CL/F was strongly influenced by eCLcr (ΔOFV= –27.9, p<0.001; ΔAIC=28). The estimation of parameters in the final model are presented in Table 5. eCLcr was calculated using a formula based on creatinine, weight, age, and gender.[23] Therefore, we compared models using eCLcr as a covariate versus using age, gender, weight, and creatinine as covariates, and found no significant differences in the parameter fitting result (Supplementary Table S2).

GOF plots for the final model are shown in Figure 1. The graph illustrates a satisfactory description of the observed data by employing the final model. The scatterplots of observed concentrations versus PRED and IPRED indicated no structural bias. The CWRES versus PRED and time exhibited a homogenous distribution around 0, and the majority of

Table 4 Prediction Error of the Individual Predictions and Population Predictions to Observations for the Evaluated Models

Model	IPRED			PRED		
	Median PE (%)	MPE (%)	RMSE (%)	Median PE (%)	MPE (%)	RMSE (%)
M1	4.04	3.03	5.93	4.26	3.06	6.35
M2	−12.12	−1.80	0.85	−89.80	−17.21	15.14
M3	−24.82	−4.71	1.50	−12.10	−0.46	4.12
M4	−19.41	−3.36	0.99	−92.89	−18.31	16.81
M5	−1.59	0.17	0.72	27.02	8.78	15.10

Abbreviations: PE, Prediction error; MPE, mean prediction Error; IPRED, individual predictions; PRED, population predictions; RMSE, Root Mean Square Error.

Table 5 Parameter Estimates and Bootstrap Results of the Final Model

	Final population parameters		**Bootstrap evaluation (n=1000 samples)**	
parameter	estimates	RSE (%)	median	95% CI
ka (1/h)	0.18 (fixed)	/	0.18 (fixed)	0.18
CL/F (1/h)	45.1	4	44.9	41.5–48.16
V/F (L)	466	20	461.6	319.5–742.0
eCLcr on CL/F	0.364	19	0.36	0.223–0.495
Interindividual variability				
CL/F	0.043	32	0.041	0.02–0.08
Residual				
Proportional residual	0.314	6	0.314	0.261–0.346

Abbreviations: RSE, relative standard error; eCLcr, estimated creatinine clearance (mL/min); CL/F, apparent clearance; Ka, absorption rate constant; V/F, apparent distribution volume.

residuals were distributed randomly within an acceptable range (−2 to 2), indicating that there is no bias in the structure of the final model, and the model is deemed acceptable. The bootstrap data further confirmed the excellent performance of the final model, as shown in Table 5. The results of pcVPC are presented in Figure 2. Most observed plots were within

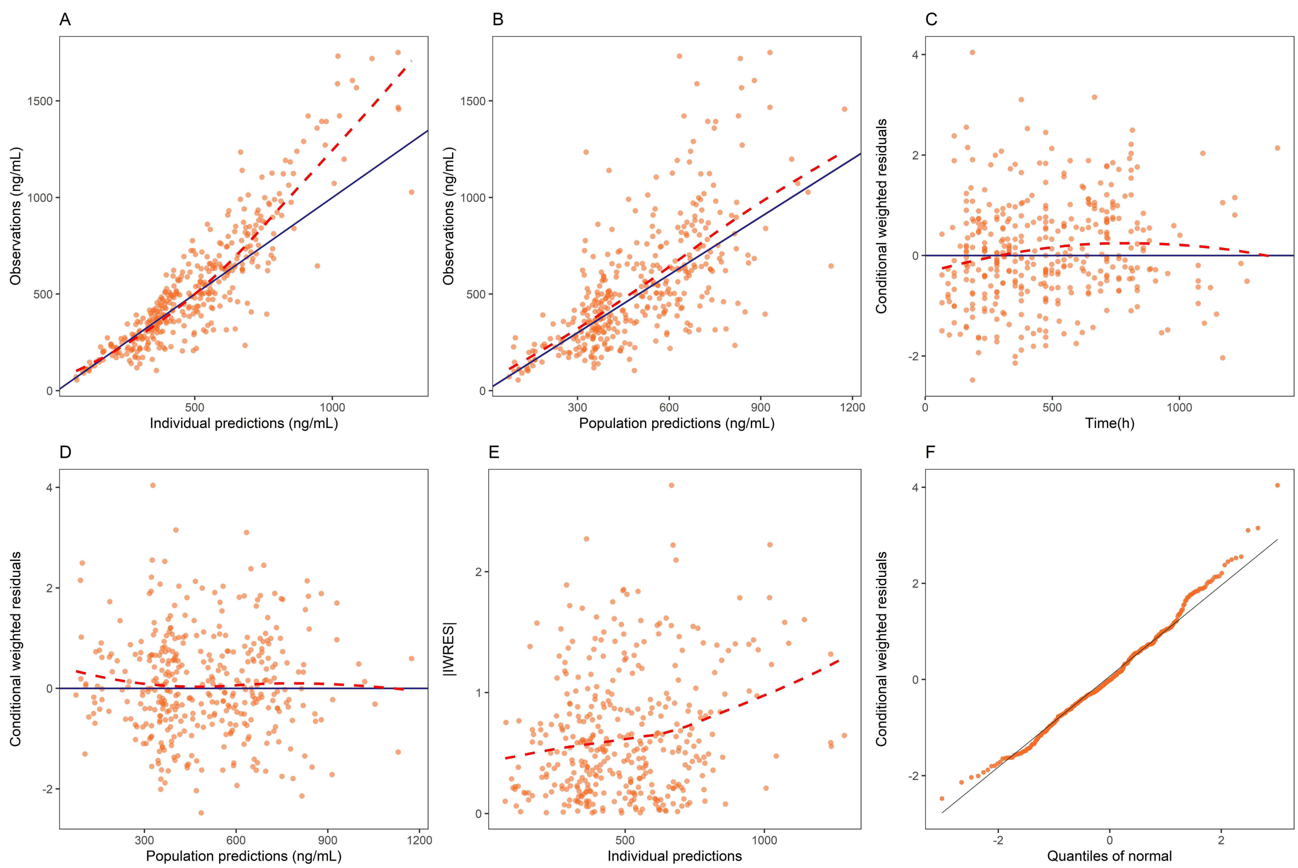

Figure 1 Goodness-of-fit plots of the final model. (**A**) Observations (OBS) versus individual predictions (IPRED). (**B**) OBS versus population predictions (PRED). (**C**) Conditional weighted residuals (CWRES) versus time after first dose. (**D**) CWRES versus PRED. (**E**) Absolute values of individual weighted residuals | IWRES | versus IPRED. (**F**) Quantile-quantile plot. The line in (**A**) and (**B**) represents the line of identity. The solid black line is the line of identity (measured = predicted) (**A,B,F**) or the reference CWRES range assuming a normal distribution (**C,D**); the dashed lines are smoothing lines through the data.

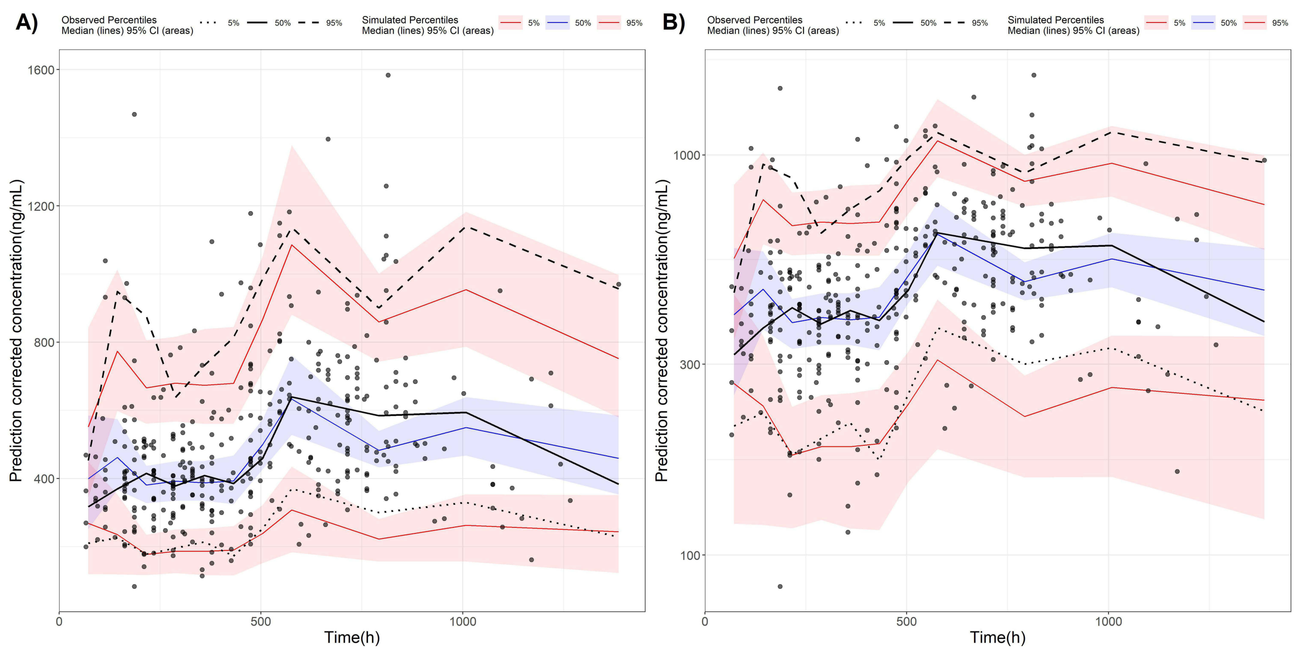

Figure 2 Visual predictive check plots of final population pharmacokinetic model. Dots are the actual observations. (**A**) With the y-axis ranging from 0 to 1600; (**B**) With the y-axis ranging from 0 to 1000.

the 90% CIs of the predicted corresponding quantiles, indicating that the final model can accurately and precisely explain the original data.

Remedial Dosing Recommendations for Poor Patient Adherence

The Monte Carlo simulation revealed a dependence of the recommended remedial regimens on the duration of delay (Supplementary Figure S5). In the event of a dose being delayed within 6 hours, it is recommended that half of the delayed dose was recommended to be taken immediately, followed by resuming the regular regimens (Strategy B). When the administration time is delayed between six and 12 hours, there are two remedial approaches: Strategy B involves giving a fractional dose first, followed by the standard full dose; whereas Strategy C entails administering the full dose initially and then topping up with a fraction of the dose. However, both strategies can present issues. With Strategy B, providing the initial partial dose could cause a rapid increase in blood drug levels, potentially leading to concentrations that exceed the safety threshold following the subsequent standard dose due to accumulation effects between doses. On the other hand, with Strategy C, administering the full dose initially might result in excessively high blood concentrations, and when a supplementary partial dose is given later—given the overall delay in the dosing schedule—it may fail to adequately maintain the drug concentration within the desired therapeutic range, thus causing it to dip below the required minimum level. Notably, when the delay time surpasses 24 hours, we recommend adopting Strategy A. This approach entails administering a standard dose at the routine programmed time with the aim to uphold the plasma drug concentrations within the desired therapeutic window.

Discussion

To the best of our knowledge, this is the first comprehensive analysis of the predictability of previously published amisulpride PopPK models. We employed prediction-based metrics and simulation-based diagnostics to evaluate the accuracy and precision of the published models. According to our findings, the existing models are inadequate for cross-center applications. Consequently, we have drawn upon the preceding studies and proceeded to optimize the modified model through the independent dataset. And, for the first time, systematically developed remedial strategies for missed or delayed doses of amisulpride through Monte Carlo simulations.

The diverse performance of the evaluated models observed in our study underscores the significance of conducting comprehensive model evaluations before their implementation in clinical settings. Although models constructed based on the Chinese population demonstrated relatively better predictive performance among all evaluated models, they fail to adequately capture the pharmacokinetics of amisulpride in cohort patients.[10,14] This can be attributed to significant variations in intrinsic factors that influence amisulpride pharmacokinetics, such as age, weight, renal impairment, and disease status, as well as extrinsic factors including concomitant medications, food, and environment. Additionally, various relevant factors such as study design, racial differences, assay methods, and modeling strategies differed across each study.[32] This underscores the limited impact of these models, which rely solely on population parameters and predetermined covariates for dose adjustment. Based on our research findings, the published models appear insufficient for cross-center application. Consequently, by leveraging an independent dataset, we have developed a new PopPK model.

Covariates can partially explain inter-individual variability, thereby enhancing the predictability of the model. We demonstrated the significant impact of eCLcr on amisulpride clearance with a one-compartment model. Some authors have suggested the use of a two-compartment model in published assessments;[11] however, our study data does not support the addition of a second compartment. In our study, the typical clearance rate of amisulpride is 45.1 L/h (average eCLcr 114.42 mL/min), consistent with prior PopPK studies.[10,13,14] Amisulpride is primarily excreted via renal filtration, with renal impairment being a major risk factor for amisulpride overexposure. In this study, eCLcr was found to better predict the clearance rate of amisulpride than serum creatinine, suggesting that estimating kidney function using the Cockcroft-Gault equation may more accurately reflect renal function than serum creatinine alone. eCLcr is one of the most widely used indicators of kidney function, calculated using a standard procedure based on weight, gender, age and creatinine. Weight is a representative of body size, and that it closely associated with the formation and activity of organs involved in drug elimination.[33] As kidney size increases within the range of 50–100 kg,[34] renal clearance is augmented in obese individuals.[35] Aging is linked to a physiological decline in glomerular filtration rate and other renal function parameters. Kidney size decreases with advancing age,[36] indicating a reduction in the number of nephrons.[37] Renal plasma flow and glomerular filtration rate decline with age.[38] Consequently, the drug clearance, which primarily remains constant in urine, decreases with age. This often necessitates dose adjustments to a certain extent as individuals grow older. The generally lower body weight, organ size, higher institutional percentage, and lower glomerular filtration rate in women are often considered physiological factors contributing to gender-related pharmacokinetic disparities.

Due to the fact that the primary elimination pathway of amisulpride is renal excretion, coupled with a low plasma protein binding rate and minimal influence from CYP enzymes, the likelihood of drug interactions involving amisulpride is very low.[3,39] Previous studies have indicated that patients on combined therapy with clozapine or lithium demonstrate unexpectedly elevated amisulpride plasma concentrations, which may be attributed to competitive mechanisms within the renal clearance pathway.[40,41] The impact of combination medication was not investigated separately due to the limited sample size, which posed challenges in assessing it as an independent covariate. Further systematic studies are required to elucidate this matter.

Although Model M2[11] relies on data from healthy elderly volunteers and Alzheimer's disease patients with psychiatric symptoms, we included it in our PopPK model library for amisulpride. This decision was made due to the limited number of published models for amisulpride, aiming to provide a comprehensive collection of models. However, during the validation, we found that despite M2 model being fitted with two compartments using densely sampled data, its performance was inferior to other models.[11] This discrepancy may be attributed to differences between the study populations, including disease type (Alzheimer's disease versus schizophrenia), disease progression, concomitant medications, and ethnic background. Additionally, the study that combined rich samples from single-dose data with trough concentration data from real world patients was best described by a two-compartment model.[11] However, a one-compartment model fit the data better than a two-compartment model in this study, as the data consisted solely of trough concentrations from clinical TDM, which lacked the additional pharmacokinetics information typically available in rich sampling data. Given the scarcity of amisulpride PopPK models use across different diseases, for models whose target populations do not fully align with the study group, external validation with available data should be conducted first.

Notably, the average plasma concentration of amisulpride observed in this study was 546.03±341.76 ng/mL, significantly exceeding the therapeutic reference range recommended by the AGNP guidelines (100–320 ng/mL).[16] The guideline's suggested concentration range is considered a useful indicator to avoid clinical non-response and extrapyramidal symptoms,

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although this recommendation is based on data from only one study where patients received a single daily dose of amisulpride ranging from 100–1550 mg.[16,30] In contrast, in routine clinical practice, amisulpride is typically administered twice daily, with doses potentially increasing to over 400 mg per day. In Chinese populations, previous studies have shown that, when using similar dose ranges (50–1200 mg/day), the plasma concentrations of amisulpride were also significantly higher than the therapeutic reference range.[10,26] Additionally, the adjusted mean dose-plasma concentration ratio (0.93±0.58 ng/mL/mg) for amisulpride exceeded the range recommended by the AGNP guidelines (0.50–0.67 ng/mL/mg).[10] Studies show that in practice, Chinese patients tend to achieve optimal clinical outcomes at higher-than-recommended plasma concentrations; furthermore, reducing the medication dose for these patients can lead to a worsening of their condition.[26,42] These findings suggest that actual dosing regimens in specific populations may lead to plasma concentration levels outside the recommended therapeutic range. Despite these observations, there is still a lack of clear pharmacokinetic-pharmacodynamic studies to determine the exposure range specifically for Chinese patients with schizophrenia.

Non-adherence to treatment regimens is a widespread issue among schizophrenia patients in mental health care.[43] Owing to the strictures of ethics, it is impractical to carry out studies involving patient non-adherence in clinical trials. Several investigations have utilized Monte Carlo simulations to explore scenarios involving medication non-adherence, particularly focusing on missed or postponed doses.[21,31,44] Notably, in the domain of schizophrenia research, these applications have thus far been confined to controlled-release formulations,[45,46] with no studies as yet extending to immediate-release preparations. Therefore, for the first time, we are employing this simulation technique to evaluate instances of non-adherence in patients with schizophrenia when using immediate-release formulations. In light of the impact that delayed or missed doses have on amisulpride's concentration-time profile, the most appropriate remedial strategy is contingent upon the delay time. When the delay in administration is between six and twelve hours, accounting for the concentration-dependent extension of the QTc interval attributed to amisulpride, Strategy C may be appropriate for patients with a background of heart failure but demonstrating relatively well-managed psychiatric conditions. For patients without such a history, Strategy B would be a more fitting approach.[47] Compared to the other strategies, Strategy D results in greater fluctuations in amisulpride concentrations and is only suitable for patients who are unable to take their next scheduled dose as prescribed. Despite our study of non-adherence based on the pharmacokinetic changes of amisulpride, previous study indicated that the decline in occupancy at central D2/3 receptors is slower than the decrease in plasma concentration.[48] This suggests that the effects of amisulpride may persist beyond the standard dosing interval, thus showing a degree of "tolerance" to incomplete adherence. However, amisulpride under conditions of non-adherence still require further exploration through more rigorous pharmacokinetic/pharmacodynamic studies.

Our study has certain limitations. Firstly, the validation dataset was retrospectively collected from a clinical setting, introducing uncertainties associated with data recording. Our data were derived from clinical TDM, and, in a majority of cases, there was only trough concentration; trough concentration can provide important information about the elimination phase of drugs, may not fully characterize the absorption and distribution properties. Therefore, in the study, we primarily relied on a one-compartment model for external validation, which may not fully capture the absorption and distribution of the drug within the body. Future studies consider using richer sample sets that include data from different pharmacokinetics phases, such as the absorption and distribution phases, to provide more details for the pharmacokinetics description of amisulpride. Secondly, we have established a remedial scheme for only a single delayed or missed dose. However, scenarios involving multiple missed doses, incorrect dosing, and other more intricate non-adherence patterns were not taken into account. Consequently, additional efforts are required to address such instances of non-compliance.

Conclusion

For the first time, we have externally validated previously published PopPK models and found that the predictive performance of the current models fails to fully capture amisulpride pharmacokinetics in an independent cohort. Consequently, we developed an improved amisulpride PopPK model. Additionally, this study evaluated the impact of medication non-adherence on amisulpride treatment, suggesting that model-based simulations could serve as a potentially effective and actionable approach to address this issue.

Ethics Approval and Consent to Participate

The investigation received ethical approval from the Xi'an Mental Health Center, and abided by the guidelines of the Declaration of Helsinki (XAJWKY-2022004 and XAJWKY-2024012). The waiver of informed consent was granted by the institutional review board for the study involves retrospective data analysis, which does not adversely affect the rights and health of the subjects. Furthermore, all patient data have been anonymized to ensure confidentiality and privacy protection.

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.

Disclosure

The authors report no conflicts of interest in this work.

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