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# Limited Predictive Performance of Existing Amisulpride PopPK Models: External Validation and Proposal of Model-Based Remedial Regimens for Non-Adherence

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## ABSTRACT

This work sought to assess how well previously published population pharmacokinetic (PopPK) models of amisulpride perform in individuals with schizophrenia using an independent dataset, and to design dosing adjustments suitable for patients who miss or delay their amisulpride doses. A comprehensive literature search of PubMed, Embase, and Web of Science was used to collect PopPK models for comparison. A total of 390 serum samples from 361 hospitalized Chinese adults diagnosed with schizophrenia were used for external evaluation. Predictive accuracy was examined using both prediction-based and simulation-based metrics. When the published models showed limited predictive quality, a revised PopPK model tailored to our cohort was built. Monte Carlo simulations were then applied to explore various non-adherence patterns and assess appropriate corrective dosing strategies.

Among the five models reviewed, four relied on trough data from schizophrenia cohorts, and one incorporated single-dose data from healthy elderly subjects together with trough levels from older individuals with Alzheimer's disease. Population and individual prediction errors spanned −92.89% to 27.02% and −24.82% to 4.04%, respectively. Simulation-based diagnostics, including NPDE, revealed systematic bias in all evaluated models. Consequently, a refined one-compartment model integrating estimated creatinine clearance (eCLcr) as a covariate influencing apparent clearance (CL/F) was derived. For delayed dosing, when the delay is ≤12 hours, half of the missed dose should be taken immediately before returning to the original schedule; if the delay approaches 24 hours, the regular dosage regimen should be resumed without compensation. Existing models do not show sufficient predictive robustness for use across different clinical centers. Prospective research will be required to substantiate the utility of our revised model before clinical implementation. Model-based simulations offered a structured method to design rational management approaches for missed or postponed doses.

**Keywords:** Population pharmacokinetics, Amisulpride, Schizophrenia, External validation, Adherence

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## Introduction

Amisulpride is an atypical antipsychotic targeting D2, D3, and 5-HT7 receptors and is valued for its strong clinical performance, notably in improving cognitive and affective symptoms with minimal metabolic complications[1]. It is effective across positive and negative symptom domains and in both acute and chronic phases of schizophrenia[2]. The drug is absorbed rapidly with a biphasic pattern: an initial peak near 1.5 hours, followed by a second peak around 3–4 hours. Its oral bioavailability is roughly 48% due to modest first-pass effects[3, 4]. Protein binding is low[3-5], and approximately 90% is eliminated renally within 24 hours, with no accumulation during repeated dosing[5]. Amisulpride is a substrate for SLC22 organic ion transporters[6], and its renal clearance is about 2.5-fold higher than expected from glomerular filtration alone[7, 8], suggesting that active secretion predominates.

Substantial inter-individual variability (IIV) has been documented and supports the clinical use of therapeutic drug monitoring (TDM)[7-9]. Factors such as age, body weight, and renal performance have been linked to PK

variability[10-14]. Compared with traditional PK analysis, PopPK enables characterization of variability using sparse TDM data, and supports prediction of individualized starting doses without requiring full sampling[15].
Although multiple PopPK models for amisulpride have been reported[10-14], they were developed within single institutions and their predictive validity has not been thoroughly tested. It therefore remains unclear whether they generalize well to other clinical settings. Given amisulpride's wide intra- and inter-patient variability, independent datasets are essential for verifying its broader applicability[16].
Adherence to antipsychotics is a key determinant of symptom control and relapse prevention[17]. Non-adherence in schizophrenia has been estimated at 56–60%, while relapse rates may reach 75–90%[18-19]. Many patients experience adherence failure during treatment, increasing the risk of symptom worsening and hospitalization[20]. Evidence suggests that improving adherence may have a greater influence on overall outcomes than many targeted interventions[21]. However, recommendations for managing missed or delayed doses remain limited, emphasizing the need for further investigation into strategies that minimize the consequences of non-adherence.
The main aim of this study was to externally evaluate existing amisulpride PopPK models using an independent cohort. If external validation indicated poor predictive performance, a secondary aim was to construct a refined PopPK model to enhance TDM-guided decision-making. Additionally, model-based simulations were performed to examine the PK impact of delayed or skipped doses and to propose practical corrective measures.

## Materials and Methods

*Literature Search*

An extensive search of the literature was performed to collect existing amisulpride PopPK models. PubMed, Web of Science, and Embase were reviewed for all studies published up to September 2023. The search terms included: ("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"). Reference lists of relevant papers were also examined for additional eligible studies. Studies were included if they: 1) investigated amisulpride; 2) were written in English; and 3) used nonlinear mixed-effects modeling approaches. Exclusion criteria were: 1) duplication; 2) insufficient data for external assessment; 3) review or methodological papers; and 4) non-parametric models. From each study, key information was extracted, including compartmental model structure, pharmacokinetic parameters, covariate relationships, inter- and intra-individual variability, residual error structure, and estimation procedures.

*Data accumulation and blood sampling*

This retrospective study compiled TDM data from 361 hospitalized individuals diagnosed with schizophrenia who received amisulpride at the Xi'an Mental Health Center from 2017 to 2021. Of these, 302 patients were on twice-daily regimens, while 59 were treated once daily. Patients were eligible if they had been taking oral amisulpride for at least 72 hours under serum concentration monitoring[22]. Demographic and clinical information was retrieved from electronic medical records, including sampling time, daily dosage, therapy duration, measured concentrations, age, sex, weight, concomitant medications, and laboratory values reflecting renal and hepatic function (uric acid, blood urea nitrogen, creatinine, total protein, albumin). Estimated creatinine clearance (eCLcr) was computed using the Cockcroft–Gault method, and eGFR using the CKD-EPI equation[23, 24].
Blood samples were obtained at 6:00 AM after a minimum of five half-lives on a stable dose to ensure steady-state conditions[25, 26]. Plasma amisulpride levels were quantified by a validated LC-MS/MS 8050 platform (Shimadzu, Kyoto, Japan). The assay's calibration curve covered 20–2000 $ng \cdot mL^{-1}$, with intra- and inter-day RSD values maintained within 5%. Recovery ranged between 80% and 120%, confirming acceptable analytical stability.

*Model evaluation*

Published models were re-implemented based on reported structural equations and parameter values. Using maximum a posteriori Bayesian estimation (MAP-BE), predicted concentrations were calculated from the dose information, sampling history, and available covariates in the validation set. When a model required covariates not present in our dataset, the mean or median values from the original publication were substituted. Both

population-level predictions and individual-specific predictions were generated at sampling times matching our clinical data.

*Prediction-based diagnostics*

Model performance was judged through both graphical and numerical assessments. Goodness-of-fit (GOF) plots compared observed concentrations (Cobs) with predicted population values (Cpred) and individual predictions (Cipred).

Accuracy and precision were quantified by calculating prediction error (PE%), mean prediction error (MPE%), and relative root mean squared error (RMSE%). In these calculations, N represents the number of amisulpride observations, while $C_{i,pred}$ and $C_{obs}$ refer to the predicted and observed concentrations for each data point, respectively[27].

$$PE = \frac{C_{i.pred} - C_{obs}}{C_{obs}} \quad (1)$$

$$MPE = \frac{1}{N}\sum_{i=1}^{N} PE \quad (2)$$

$$RMSE = \sqrt{\frac{1}{N}\sum_{i=1}^{N} PE^{2}} \quad (3)$$

*Simulation-based diagnostics*

Model predictive ability was examined using prediction-corrected visual predictive checks (pcVPC). For each candidate model, 1000 simulated datasets were generated and compared with the observed concentrations to judge predictive consistency. The pcVPC allowed visual comparison of amisulpride concentration–time profiles by evaluating the 5th percentile, median, and 95th percentile trends against observed values.

Population-level predictive accuracy was also investigated through normalized prediction distribution errors (NPDE). NPDE values were produced for the validation dataset using 1000 simulations from the final model, computed with the NPDE package (version 2.0). Graphical assessments and statistical testing were applied to compare NPDE distributions with the theoretical reference. The Wilcoxon signed-rank test ($H_0$: mean = 0), Fisher's variance test ($H_0$: variance = 1), and the Shapiro–Wilk test ($H_0$: normality) were used.

*PopPK model development and validation*

Amisulpride PopPK modeling was performed using nonlinear mixed-effects analysis in NONMEM® (version 7.4.0, ICON Development Solutions, Ellicott City, MD, USA). One-compartment and two-compartment model structures were evaluated. Parameter estimation employed the first-order conditional estimation with interaction method (FOCE-I). Revisions to the base model were focused on structures showing strong predictive performance. Because the dataset mainly contained trough concentrations following chronic dosing, absorption parameters could not be robustly estimated. Thus, based on prior publications with good predictive behavior and accounting for similarities within the Chinese population, the absorption rate constant (Ka) was fixed at 0.18[7-13]. Inter-individual variability (IIV) for structural parameters assumed log-normal distributions, using the exponential model:

$$P_i = P_{TV} \times \mathrm{Exp}(\eta_i) \quad (4)$$

where $P_i$ denotes the parameter for the ith subject, PTV the typical population value, and $\eta_i$ a random term with mean zero and variance $\omega^2$.

Residual variability was explored under additive, proportional, and combined error forms:

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, $C_{obs}$ is the measured concentration, $C_{pred}$ the corresponding model-predicted value, and $\varepsilon_{add}$ and $\varepsilon_{prop}$ are normally distributed error terms (mean = 0, variance = $\sigma^2$).

Covariates were evaluated using forward selection and backward elimination [28]. A covariate was added when the decrease in objective function value (OFV) exceeded 6.64 ($P < 0.01$). During backward elimination, a covariate remained only if its removal increased OFV by more than 10.83 ($P < 0.001$). Akaike's Information Criterion (AIC) was also computed to evaluate the trade-off between improved fit and model simplicity, with lower AIC indicating superior parsimony.

Model adequacy was further evaluated through GOF plots, bootstrap analysis, and VPC. Bootstrapping was performed by generating 1000 replicate datasets via resampling. Parameter estimates from the final model were compared with bootstrap medians and 95% confidence intervals. Consistency between these results indicated strong stability of the final model [29].

*Nonadherence scenarios and remedial strategies*

To enhance clinical practicality, recommendations suggest that when a dose is missed or delayed, the corrective dosing should involve two administration points: the moment the patient realizes the omission and the upcoming scheduled dose [30, 31]. Based on this principle, several remedial strategies were examined:

Strategy A: take the full missed dose immediately, followed by the usual dose at the next planned administration.

Strategy B: take a reduced dose right away, then take the regular scheduled dose at the next dosing time.

Strategy C: take the standard dose immediately, then a reduced amount at the next scheduled dose.

Strategy D: take both the partial and regular doses at once; skip the next scheduled dose, then return to the routine dosing plan.

Strategy E: take both the reduced and full doses together immediately, then continue the normal regimen without skipping the next dose.

Strategy F: take twice the standard dose immediately, then resume the normal dosing routine.

The individualized therapeutic window—defined as the interval between the 5th percentile trough and the 95th percentile peak concentration at steady state for a specific dose—was used to determine optimal exposure. The proportion of time that simulated concentrations remained within this window served as the primary metric for comparing the effectiveness of each strategy.

## Results and Discussion

*Dataset profiles*

**Table 1** presents demographic and clinical characteristics. In total, 390 concentration measurements were collected from 361 individuals. The average patient age was 32 years (range 18–67), and the mean body weight was 62 kg (range 40–109 kg). Amisulpride plasma levels varied from 54.7 to 1955.7 ng/mL. Daily doses ranged from 200 to 2000 mg, with a median of 600 mg.

**Table 1.** Characteristics of the External Validation Dataset

| Characteristic | Median (Range) | Mean ± SD |
|---|---|---|
| Number of patients (Male/Female) | – | 361 (150/211) |
| Number of serum samples | – | 390 |
| Age (years) | 32 (18 – 67) | 34.42 ± 10.56 |
| Body weight (kg) | 62 (40 – 109) | 62.93 ± 11.71 |
| Daily amisulpride dose (mg) | 600 (200 – 1200) | 555.90 ± 192.56 |
| Measured amisulpride concentration (ng/mL) | 471.8 (54.7 – 1955.7) | 546.03 ± 341.76 |
| Dose-normalized concentration (ng/mL per mg) | 0.88 (0.17 – 3.26) | 0.970 ± 0.474 |
| Uric acid (µmol/L) | 297 (81 – 698.9) | 305.03 ± 89.86 |
| Blood urea nitrogen (mmol/L) | 3.5 (0.6 – 10.1) | 3.72 ± 1.37 |
| Serum creatinine (µmol/L) | 60 (30 – 148.9) | 66.34 ± 15.7 |
| Estimated creatinine clearance (mL/min) | 114.42 (23.29 – 239.51) | 116.7 ± 33.53 |

| | | |
|---|---|---|
| Estimated GFR (mL/min/1.73 m²) | 118.5 (79.9 – 146.5) | 117.7 ± 10.4 |
| Total protein (g/L) | 67 (50 – 95.3) | 67.56 ± 6.83 |
| Albumin (g/L) | 40 (30 – 64) | 40.8 ± 4.7 |

Abbreviations: UA, uric acid; Cr, creatinine; eCLcr, creatinine clearance (Cockcroft–Gault); eGFR, estimated glomerular filtration rate (CKD-EPI without race); TP, total protein; ALB, albumin; SD, standard deviation.

*Literature search and summary of published popPK models*

A total of five publications describing amisulpride PopPK models were identified. These five models (M1–M5) were included for external testing [10-14]. Population and clinical features for each study are provided in **Table 2**. Three models originated from Chinese patient cohorts [10, 13, 14], while the others were developed in France/UK [11] and Switzerland [12].

Key model attributes are listed in **Table 3**. Four studies described amisulpride disposition using a one-compartment model, whereas one investigation applied a two-compartment structure [11]. Estimated clearance values across the studies ranged from 32.6 to 61.1 L/h. For one-compartment models, reported distribution volumes ranged between 391 and 1720 [10-13]. All models incorporated inter-individual variability on clearance, with estimates between 3.03% and 36.0% [10, 11] Significant covariates influencing CL/F across studies included age, body weight, eCLcr, and eGFR. Residual variability was modeled using additive, proportional, or mixed error structures, including additive error applied to log-transformed data.

**Table 2.** Characteristics of the Included PopPK Investigations

| Model (Publication Year) | Study Design | Country/Region | Population | No. of Subjects (M/F) | Age (years) Mean ± SD or Median [Range] | Body Weight (kg) Mean ± SD or Median [Range] | Serum Creatinine (µmol/L) Mean ± SD or Median [Range] | eCLcr (mL/min) Mean ± SD or Median [Range] | eGFR (mL/min/1.73 m²) | No. of Observations | Sampling Strategy | Daily Dose (mg) Mean ± SD or Median [Range] | Analytical Method [LOQ] (ng/L) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **M1** Wei L. (2023)[10] | Retrospective | China | Psychiatric inpatients | 88 (69/19) | 35.23 ± 10.7 | 68.12 ± 13.9 | 75.77 ± 14.98 | 114.30 ± 31.25 | NR | 168 | Steady-state trough concentrations | 681.55 ± 222.84 | 2D-LC–UV [12] |
| **M2** Suzanne R. (2016)[11] | Open observational | France, UK | Study 1: Healthy elderly Study 2: Alzheimer's disease patients | Study 1: 20 (10/10) Study 2: 41 (25/16) | Study 1: 68.7 ± 4.1 Study 2: 82 ± 6.6 | Study 1: 66.6 ± 9.1 Study 2: 68.0 ± 15.2 | Study 1: 56 ± 10.2 Study 2: 83.1 ± 25.7 | Study 1: 80.5 ± 17.5 Study 2: 67.7 ± 17.3 | NR | Study 1: 280 Study 2: 41 | Study 1: Serial sampling (0–72 h post single dose) Study 2: Steady state | Study 1: 50 mg (single) Study 2: 49.4 ± 11.2 | Study 1: HPLC [0.5] Study 2: LC-MS/MS [9] |
| **M3** Anaïs G. (2019)[12] | Retrospective | Switzerland | Schizophrenia or schizotypal disorder patients | 242 (132/110) | 37 [18 – 91]* | 75 [43 – 185]* | 76 [44 – 167]* | 93 [20 – 180] | NR | 513 | Median 13.3 h (0.05–58 h) post-dose (mainly trough) | 600 [50 – 2000] | HPLC-MS [1] |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **M4** Shanqing H. (2021)[13] | Retrospective | China | Psychiatric inpatients | 121 (58/63) | 35.83 ± 13.50 | 62.73 ± 12.86 | 65.05 ± 16.61 | NR | NR | 330 | Steady-state trough concentrations | NA | HPLC-MS [NR] |
| **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]* | NR | 114 [101 – 130]* | 2328 | Trough concentrations | 566 ± 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, creatinine clearance; 2D-LC–UV, two-dimensional LC with ultraviolet detection; HPLC, high-performance liquid chromatography; LC-MS/MS, liquid chromatography–tandem mass spectrometry; HPLC-MS, high-performance LC–mass spectrometry; UPLC-MS/MS, ultra-performance LC–MS/MS; LOQ, limit of quantification; NR, not reported.

**Table 3.** Modeling Approaches and Final Pharmacokinetic Estimates in the Reviewed Studies

| Model (Publication Year) | Software & Estimation Method | Structural Model | Key Fixed-Effect Parameter Estimates | Inter-individual Variability (IIV) on CL/F or CL | Residual Variability | Internal Evaluation Methods | External Validation (N = samples) | Primary Model Application |
|---|---|---|---|---|---|---|---|---|
| **M1** Wei L. (2023)[10] | NONMEM (FOCE-I) | 1-compartment, first-order absorption & elimination | CL/F (L/h) = 32.6 × (eCLcr / 114.3)^0.485 V/F = 391 L Ka = 0.9 $h^{-1}$ (fixed) | 3.03% | Proportional: 4.87% | GOF plots, bootstrap, NPDE | NR | – |
| **M2** Suzanne R. (2016)[11] | Monolix (NLME) | 2-compartment, mixed absorption | CLi = 54.3 × (agei/76)^ −2.9 × (weighti/70)^0.75 L/h V1 = 455 L Q = 111 L/h V2 = 736 L Ka = 0.85 $h^{-1}$ | 36% (Group 1) 43% (Group 2) | Proportional: 13% (Group 1) 53% (Group 2) | VPC | NR | Dosing recommendations based on trough concentrations |
| **M3** Anaïs G. (2019)[12] | NONMEM + PsN Toolkit (NLME) | 1-compartment, first-order absorption & elimination | CL (L/h) = 43.9 × (1 – 0.47 × ((age – 37)/37)) × (1 + 0.53 × ((LBW – 52)/52)) V = 926 L Ka = 0.9 $h^{-1}$ (fixed) | 34% (CL) 58% (V) | Proportional: 53% | VPC, bootstrap | NR | Dosing recommendations based on trough concentrations |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **M4** Shanqing H. (2021)[13] | NONMEM (FOCE-I) | 1-compartment, first-order absorption & elimination | CL/F = 1.04 × (AGE/32) ^−0.624 L/h V/F = 1720 L Ka = 0.18 $h^{-1}$ | 30.10% (CL/F) 122.50% (V/F) | Proportional: 6.4% | GOF plots, bootstrap, NPDE | NR | Dosing recommendations based on trough concentrations |
| **M5** Anning L. (2023)[14] | NONMEM (FOCE-I) | 1-compartment, linear elimination | CL/F = 60.5 × (eGFR/113.87)^0.817 L/h V/F = 645 L Ka = 0.106 $h^{-1}$ | 35.90% (CL/F) 130.90% (V/F) | Proportional: 34.6% | GOF plots, bootstrap, NPDE | N = 145 | Dosing recommendations based on trough concentrations |

Abbreviations: CL, apparent clearance (L/h); Q, inter-compartmental flow; V, distribution volume (L); Ka, absorption rate constant ($h^{-1}$); eCLcr, estimated creatinine clearance; eGFR, estimated glomerular filtration rate; NONMEM, nonlinear mixed-effects method; FOCE, first-order conditional estimation; FOCE-I, FOCE with interaction; CMT, compartment; FO, first-order; NLME, nonlinear mixed-effects; PSN, Perl-speaks-NONMEM; GOF, goodness-of-fit; VPC, visual predictive check; NPDE, normalized prediction distribution errors; prop, proportional error; NR, not stated.

*Model evaluation*

Because lean body mass used in Model M3 was absent in our dataset, the value was set to the original study's median (52) for assessment. For population-level estimates, Model M2 [11] produced clear underprediction relative to actual concentrations, while Model M5 [14] displayed consistent overprediction. For individual-level fits, Models M2 [11] and M4 [13] tended to generate values below the observations, and Model M3 [12] showed a similar downward deviation. Model M1[10] was the only one yielding reliable agreement for both individual and population outputs.

Diagnostic summaries **(Table 4)** indicated that Models M1 [10] and M5 [14], each meeting thresholds of Median PE ≤ 30%, MPE ≤ 20%, and RMSE ≤ 20%, performed better than the remaining models. Model M1[10] was the most accurate overall, achieving Median PE ≤ 10%, MPE ≤ 10%, and RMSE ≤ 10%. Only Model M3 [12] showed individual Median PE values outside ±20%. For population predictions, Models M2 [11] and M4 [13] exceeded ±20% Median PE, giving the largest systematic errors. All models showed acceptable ranges for MPE and RMSE [10-14].

**Table 4.** Error Metrics for Individual and Population Predictions Across 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 prediction; PRED, population prediction; RMSE, root mean square error.

Simulation-based checks revealed non-normal NPDE distributions for every model. Bias related to time and predicted concentrations was also noticeable. The global statistical evaluation gave corrected p-values < 0.001 for all models, showing that none satisfied simulation-based diagnostic criteria [10-14].

The pcVPC findings demonstrated variable mismatches between empirical and simulated datasets in all reports. Both over- and under-projection appeared across the models [10-14]. Model M5 [14] showed comparatively better agreement: although the 5th percentile of observed values did not align perfectly with simulated bands, the observed 50th and 95th percentiles generally fell inside the simulation confidence limits.

*PopPK model development and validation*

Amisulpride kinetics were most suitably represented using a single-compartment model with first-order input and elimination. Differences between medication groups prevented concomitant drug use from functioning as a covariate. Demographic factors, biochemical data, and daily dose were evaluated for inclusion. After stepwise testing, eCLcr showed a major influence on CL/F (ΔOFV = –27.9, $p < 0.001$; ΔAIC = 28). Final parameter values are listed in **Table 5**. eCLcr was derived from weight, age, sex, and serum creatinine [23]. When comparing a model using eCLcr with one using these four variables separately, fits were essentially unchanged.

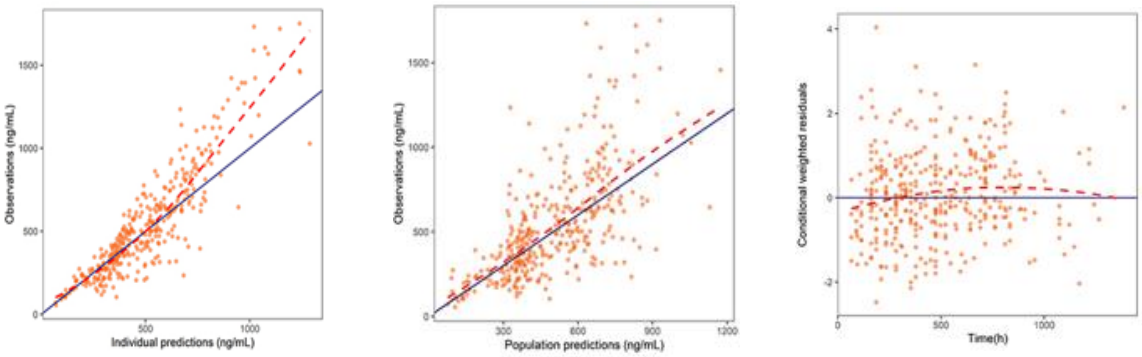
**Table 5.** Final Model Parameters and Bootstrap Results

| Parameter | Final population values | Bootstrap assessment | |
|---|---|---|---|
| | Estimate | RSE (%) | Median |
| **ka (1/h)** | 0.18 (fixed) | – | 0.18 (fixed) |
| **CL/F (1/h)** | 45.1 | 4 | 44.9 |
| **V/F (L)** | 466 | 20 | 461.6 |
| **Effect of eCLcr on CL/F** | 0.364 | 19 | 0.36 |
| **Between-subject variability** | | | |
| **CL/F** | 0.043 | 32 | 0.041 |
| **Residual variability** | | | |
| **Proportional error** | 0.314 | 6 | 0.314 |

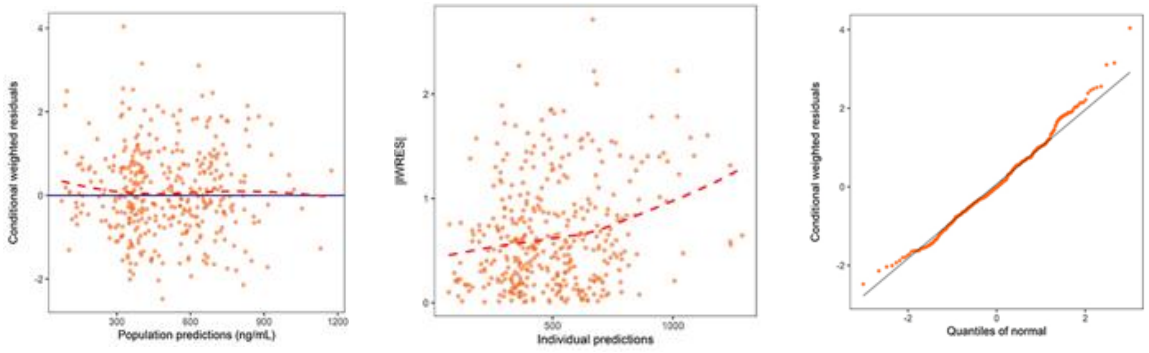
Abbreviations: RSE, relative standard error; eCLcr, estimated creatinine clearance (mL/min); CL/F, apparent clearance; Ka, absorption rate constant; V/F, distribution volume.

*GOF plots for the final model*

**Figure 1** displays the goodness-of-fit outputs for the finalized model. Overall, the model reproduced the observed concentration data well. Scatterplots comparing observations with both PRED and IPRED showed no systematic deviation. CWRES plotted against PRED and time were centered around zero with a uniform spread, and most values stayed within the −2 to 2 interval, supporting the absence of structural bias and confirming that the model performs reliably. Bootstrap replication results, summarized in **Table 5**, further validated the robustness of the final model. The pcVPC results, depicted in **Figure 2**, demonstrated that the majority of observed data points fell within the 90% prediction intervals for the corresponding quantiles, indicating strong predictive accuracy and precision.

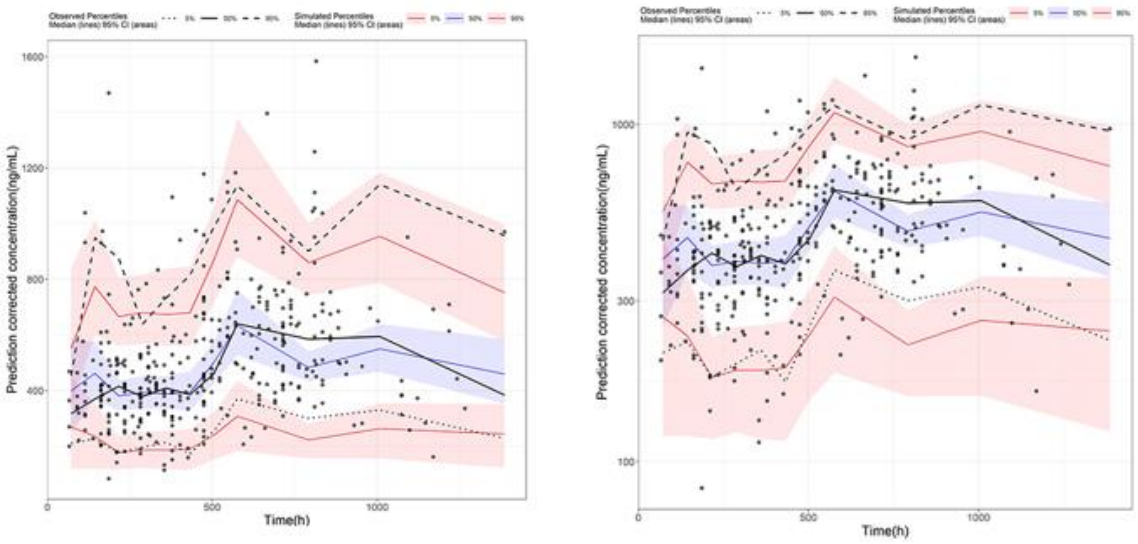



a) b) c)




d) e) f)

**Figure 1.** Goodness-of-fit visualization for the final model.
(a) OBS vs IPRED. (b) OBS vs PRED. (c) CWRES vs time following the initial dose. (d) CWRES vs PRED. (e) |IWRES| vs IPRED. (f) Q–Q plot.
In panels (a) and (b), the solid line represents the identity line. In panels (c) and (d), the solid curves depict the expected CWRES limits assuming normality, while dashed curves show smoothed trends through the data.




a) b)

**Figure 2.** Visual predictive check for the final PopPK model.
(a) y-axis 0–1600. (b) y-axis 0–1000.

*Remedial dosing recommendations for poor patient adherence*

Monte Carlo simulations indicated that the optimal corrective action depends on how long the dose was delayed. If the delay is under 6 hours, taking half of the missed dose immediately and then returning to the routine schedule (Strategy B) is advised. For delays between 6 and 12 hours, two alternatives were identified: Strategy B (partial dose first, then a full scheduled dose) or Strategy C (full dose first, then a partial subsequent dose). Both approaches have drawbacks. With Strategy B, beginning with a fractional dose may cause a rapid concentration rise, and the next full dose could push levels past the safety margin due to accumulation. With Strategy C, the initial full dose may produce overly high concentrations, while the later partial dose—given after an already late interval—may not adequately sustain concentrations within the therapeutic window, increasing the risk of subtherapeutic levels. When the delay exceeds 24 hours, Strategy A is recommended, i.e., administering the routine full dose at the next planned dosing time to maintain appropriate plasma exposure.

To our knowledge, this work represents the first in-depth examination of how well previously published amisulpride PopPK models perform in terms of predictability. We assessed their precision and accuracy using both prediction-based criteria and simulation-oriented diagnostics. Our analyses indicate that these established models do not translate effectively across different clinical centers. As a result, we used insights from prior

research along with an independent cohort to refine a revised model. Additionally, we systematically formulated dosing-remediation strategies for missed or delayed administrations of amisulpride using Monte Carlo simulation, which has not been reported before.

The wide variability in model performance observed here highlights the necessity of rigorous evaluation before adopting a PopPK model in practice. Although models developed within Chinese cohorts tended to outperform the others, they still failed to adequately describe pharmacokinetics in the present patient group [10-14]. This likely reflects substantial differences in intrinsic determinants—age, body mass, renal dysfunction, underlying conditions—as well as extrinsic influences including diet, concurrent drugs, and environmental factors. Study-specific distinctions such as sampling schemes, racial distribution, analytical platforms, and modeling techniques also contribute to the inconsistency [32]. Consequently, models that rely predominantly on preset population parameters and predetermined covariates may offer limited generalizability. Based on these findings, previously published models appear unsuitable for direct cross-center implementation. Therefore, we constructed a new PopPK model with the assistance of an independent dataset.

Covariates help explain between-subject variability and strengthen predictive capability. In our analysis, eCLcr had a pronounced effect on amisulpride clearance within a one-compartment framework. Although some reports favored a two-compartment system [11], our data did not justify such an expansion. The estimated clearance of 45.1 L/h (with an average eCLcr of 114.42 mL/min) aligns well with earlier PopPK estimates [10, 13, 14], Since amisulpride is mainly eliminated renally, diminished kidney function substantially increases exposure. Here, eCLcr was superior to serum creatinine in describing changes in clearance, suggesting that the Cockcroft–Gault calculation provides a more accurate representation of renal performance than creatinine alone. eCLcr remains one of the most widely utilized indicators of renal capacity and incorporates body weight, sex, age, and creatinine. Body mass reflects overall size and correlates with the functioning of organs involved in elimination [33] As body size rises toward the 50–100 kg range [34], renal clearance tends to increase, particularly in individuals with obesity [35]. Aging, however, is associated with progressive reductions in glomerular filtration and other renal metrics; kidney volume declines [35, 36] alongside nephron loss [37], and renal plasma flow also decreases [38]. Consequently, drug elimination via the kidneys generally diminishes with age, often requiring dose reductions. Differences in body composition, organ size, institutional rates, and filtration capacity in women further contribute to sex-specific pharmacokinetic variation.

Because amisulpride is primarily cleared renally, binds weakly to plasma proteins, and is minimally affected by CYP pathways, its potential for drug–drug interactions is low [3, 39]. Nevertheless, unusually high amisulpride levels have been reported in patients receiving clozapine or lithium, possibly due to competitive inhibition within renal elimination mechanisms [40, 41]. In the current analysis, combination therapy could not be thoroughly evaluated as an independent covariate due to limited sample availability. More comprehensive investigations are needed to clarify these interactions.

Although Model M2_11 was originally derived from data collected in healthy older adults and individuals with Alzheimer's disease experiencing psychiatric manifestations, we still incorporated it into the amisulpride PopPK model repository. This inclusion aimed to ensure a broad model spectrum, given the very limited number of published amisulpride models. During external assessment, however, we noted that the M2 model—despite being established using dense sampling and a two-compartment structure—performed worse than several other candidates [11]. Such discrepancies likely reflect distinctions among study cohorts, including diagnostic category (Alzheimer's disease versus schizophrenia), differing illness trajectories, concomitant drug use, and ethnic composition. Another previous analysis combining intensive single-dose sampling with trough data from real-world patients favored a two-compartment description [11]. In contrast, the present dataset, which consisted exclusively of trough measurements obtained through routine TDM, was more accurately characterized by a one-compartment structure due to the absence of rich PK information. Because available amisulpride PopPK models arise from heterogeneous clinical settings, models derived from populations misaligned with the target cohort should undergo external confirmation before being applied.

A noteworthy finding in our dataset was the mean amisulpride plasma level of 546.03 ± 341.76 ng/mL, which was far above the AGNP guideline's recommended therapeutic interval (100–320 ng/mL) [16]. The recommended range is intended to minimize inadequate response and extrapyramidal symptoms, although it was derived from a single investigation involving once-daily administration of 100–1550 mg amisulpride [16, 30]. In contrast, routine practice commonly uses twice-daily dosing, with some regimens exceeding 400 mg/day. Studies in Chinese cohorts receiving comparable daily doses (50–1200 mg/day) similarly demonstrated concentrations surpassing

this suggested range [10, 26]. Moreover, the adjusted mean dose-normalized concentration (0.93 ± 0.58 ng/mL/mg) was higher than the guideline-indicated target (0.50–0.67 ng/mL/mg) [10]. Evidence further indicates that Chinese patients frequently obtain optimal improvements at plasma levels above the standard therapeutic range, and downward dose adjustments may aggravate symptoms [26, 42]. Collectively, these findings imply that population-specific dosing patterns often yield concentrations outside guideline limits. Nevertheless, well-designed PK–PD studies to define exposure thresholds for Chinese individuals with schizophrenia remain lacking. Poor adherence remains one of the most prevalent obstacles in the long-term management of schizophrenia [43]. Ethical constraints preclude formal clinical trials intentionally inducing non-adherence. Consequently, multiple studies have applied Monte-Carlo-based simulations to mimic missed or delayed doses [21, 31, 44]. Prior schizophrenia-focused simulation work has almost exclusively addressed controlled-release formulations [45, 46], with no comparable evaluations of immediate-release preparations. Our study is therefore the first to apply this approach to non-adherence scenarios involving immediate-release amisulpride. The appropriate corrective action following a missed dose depends on the length of the delay, particularly given amisulpride's concentration-related influence on QTc prolongation. When dosing is postponed by six to twelve hours, Strategy C may be preferable for patients with existing heart-failure risk but stable psychiatric control, whereas Strategy B is likely more suitable for individuals without cardiac history [47]. Strategy D produces the largest swings in drug exposure and should be reserved only for circumstances in which the next scheduled dose cannot be taken. Although our evaluation relied strictly on pharmacokinetic behavior, prior work suggests that dissociation of amisulpride from central D2/3 receptors occurs at a slower rate than its plasma elimination [48]. This indicates that therapeutic effects may persist longer than plasma levels would suggest, offering some degree of "buffering" against imperfect adherence. Even so, the consequences of missed or delayed doses for amisulpride still require more robust PK–PD investigations. Our study has certain limitations.

First, the validation cohort originated from retrospectively gathered data in a real-world clinical environment, which naturally introduces variability linked to documentation practices. Because the information came from routine TDM, most records contained only trough levels; although such measurements reflect drug elimination, they provide limited insight into absorption and distribution. As a result, we mainly applied a one-compartment model for external assessment, a simplification that may not fully represent the drug's behavior across different kinetic phases. Future investigations should employ more comprehensive sampling that spans absorption, distribution, and elimination to produce a more detailed PK characterization of amisulpride. Second, our corrective strategy was constructed solely for a single missed or delayed dose. More complex patterns of non-adherence—such as repeated omissions, dosing errors, or other irregular behaviors—were not incorporated. This highlights the need for further methodological expansion to manage these broader adherence issues.

## Conclusion

This work presents the first external evaluation of existing PopPK models for amisulpride and shows that their predictive capacity does not adequately describe the pharmacokinetic profile in an independent dataset. In response, we created an enhanced PopPK framework. We also examined how deviations from prescribed dosing influence amisulpride therapy, indicating that simulation-driven strategies may offer a practical and useful tool for mitigating adherence-related challenges.

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