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Research article

Population pharmacokinetic approach to guide personalized sertraline treatment in Chinese patients

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ABSTRACT

Object: Sertraline is a first-line SSRI for the treatment of depression and has the same effectiveness along with a superior safety profile compared to other medications. There are few population pharmacokinetic (PPK) studies of sertraline and a lack of studies in the Chinese population. Therefore, we performed a PPK analysis of Chinese patients treated with sertraline to identify factors that can influence drug exposure. In addition, the dosing and discontinuation regimen of sertraline when applied to adolescents was explored. **Methods:** Sertraline serum drug concentration data were collected from 140 hospitalized patients to generate a sertraline PPK dataset, and data evaluation and examination of the effects of covariates on drug exposure in the final model were performed using nonlinear mixed-effects models (NONMEM) and first-order conditional estimation with interaction (FOCE-I). Examining rational medication administration and rational withdrawal of sertraline based on significant covariates and final modeling. **Results:** A one-compartment model with first-order absorption and elimination of sertraline was developed for Chinese patients with psychiatric disorders. Analysis of covariates revealed that age was a covariate that significantly affected sertraline CL/F ($P < 0.01$) and that sertraline clearance decreased progressively with aging, whereas other factors had no effect on CL/F and V/F of sertraline. In the age range of 11–79, there were 54 adolescent patients (about 1/3) aged 13–18 years, and the safe and effective optimal daily dose for adolescent patients based on the final model simulations was 50–250 mg/d. For adolescent patients, serum concentration fluctuations were moderate for OD doses of 50 mg and 100 mg, using a fixed dose-descent regimen. For patients with OD doses of 150–200 mg and BID doses of 100–200 mg, a more gradual decrease in serum concentration was achieved with a fixed dose interval of 7 or 14 days for 25 mg as the regimen of descent. **Conclusions:** To our knowledge, this may be the first PPK study of sertraline in Chinese patients. We found that age was an important factor affecting clearance in Chinese patients taking sertraline. Patients taking sertraline may be exposed to increased amounts of sertraline due to decreased clearance with increasing age. The rational dosing and safe

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discontinuation of sertraline in adolescent patients can be appropriately referenced to the results of the model simulation, thus providing assistance for individualized dosing in adolescents.

1. Introduction

Mental illness, especially depression, has affected an increasing number of people worldwide in the last decade as social and economic development has greatly burdened healthcare services [1]. Current treatment methods include medication, psychotherapy, and exercise, but medication is still the primary treatment for the vast majority of mental illnesses [2]. Sertraline is a highly selective 5-hydroxytryptamine reuptake inhibitor (SSRI) that is effective in the treatment of a wide range of psychiatric disorders, including major depressive disorder (MDD), panic disorder, generalized social anxiety disorder, obsessive-compulsive disorder (OCD) [3,4]. Since its approval for sale in the United States in 1991, sertraline has been one of the favored SSRIs for the treatment of depression [5]. Sertraline is considered an antidepressant that can be used in children, adolescents, and pregnant women [6,7] because of its unique advantages in safety, efficacy, and tolerability and is also the drug of choice for the treatment of depression in clinical settings [8].

Sertraline is routinely administered at doses of 25–200 mg/d for depression, anxiety, OCD, and other disorders and conditions [9,10], but pharmacokinetic studies have shown that even when sertraline is administered at doses of up to 400 mg, a linear relationship between dose and concentration is maintained [11]. Sertraline is metabolized by several CYP450 enzymes, including CYP2B6 and CYP2C19 [12,13], resulting in the formation of N-desmethyl sertraline, a metabolite with only 1/10 of the original drug activity. As a highly polymorphic enzyme, single nucleotide polymorphisms (SNP) in CYP2C19 lead to inter-individual differences in pharmacokinetics and pharmacodynamics [14,15]. The maximum plasma drug concentration of sertraline is reached about 6 h after oral administration of 200 mg/day, and it has a slow drug absorption with a half-life of about 24 h [16]. Sertraline has a long half-life (approximately 24 h) and high plasma protein binding (approximately 95 %) [17]. Available relevant studies have shown that age, gender and genotype and liver function can influence the pharmacokinetics of sertraline [8,14,18,19].

To the best of our knowledge, two population pharmacokinetic studies of sertraline have been published, but there is no population pharmacokinetic study of sertraline in the Chinese population. Therefore, this study aimed to develop a PPK model of sertraline in Chinese patients and to explore the factors affecting sertraline exposure using retrospectively collected data on sertraline serum concentrations in patients, in order to provide suggestions and references for the rational use of sertraline in the Chinese population.

2. Material and methods

2.1. Patients and data sources

To evaluate the impact of these variables on sertraline pharmacokinetics, this study retrospectively gathered data on age, gender, height, weight, body mass index (BMI), and combination medications (such as lamotrigine, quetiapine, and venlafaxine) from patients with psychiatric disorders at the Brain Hospital of Guangzhou Medical University from 2018 to 2022. Patients also had to adhere to the requirement that sertraline serum concentrations be monitored while they were in the hospital and that they have non-zero concentration data at least at two separate dosages. Additionally, this study received permission from the Affiliated Brain Hospital of Guangzhou Medical University's Institutional Review Board (approval number: 2021027).

2.2. Determination of sertraline serum concentration

In a PR coagulation tube, transfer 3–5 ml of the patient's venous blood, and centrifuge at 14,500 g for 5 min. After centrifugation, add 500 μL of acetonitrile mix and 20 μL of the internal standard mix (sertraline–d3) to 100 μL of the supernatant in an Eppendorf tube. Subsequently, vortex mix for about 15 s, centrifuge at 21,500 g for 5 min, remove 100 μL of supernatant and transfer to an autosampler with a liner tube. The sertraline assay used was LC-MS/MS (Shimadzu, Japan), and the assay was methodologically validated for selectivity, specificity, matrix effects, stability, intra- and inter-batch precision, and accuracy. Using an Agilent Eclipse XDB-C18 column with a mobile phase ratio of (A) 75 % methanol to 5 mM ammonium formate and (B) methanol, separation conditions were carried out. The procedure took 1 min at a flow rate of 0.6 ml/min (injection volume: 1 μL) and had a linear range of 5–500 ng/ml.

2.3. PPK modeling

A PPK model for sertraline was developed using a nonlinear mixed-effects modeling program (NONMEM, version 7), and its parameters and potential covariates were estimated using a one-compartment model with first-order conditional estimation with inter- and intra-individual variance interactions (FOCE-I). Pirana (version 2.9.0) was used to construct and validate the model. The results of the normalized predictive distribution error (NPDE) test were plotted using the NPDE package in R (version 4.2.2). Perl-speaks NONMEM (version 3.4.2) was used to perform bootstrap analysis (n = 1000). Fitted effect plots were performed with GraphPad Prism (version 9). Statistical analyses were performed using SPSS (version 27.0).

A basic model without any covariates was initially developed. The serum collected was the trough concentration of the elimination phase, so the model used a one-compartment model with first-order absorption and first-order elimination for the pharmacokinetic

parameters, i.e., apparent oral clearance (CL/F), apparent volume of distribution (Vd/F), and absorption rate. The absorption phase could not be evaluated because serum concentration data for the absorption phase were not available. The absorption rate constant (Ka) was fixed at 0.098 according to the model developed in the relevant research [20]. The following are the exponential error model (Eq. (1)) used to describe the interindividual variability (IIV) and the residual error variability model (Eq. (2)) for unexplained intraindividual variability.

$$P_i = \widehat{P} \times e^{\eta_i} \tag{1}$$

$$Y = F \times (1 + \varepsilon_1) + \varepsilon_2 \tag{2}$$

In Eq. (1), P_i denotes the individual parameter values, denotes the population parameter values, and η_i denotes the random effect of each individual with a normal distribution with mean 0 and variance ω^2. In Eq. (2), Y and F denote the observed and model predicted values of sertraline concentration, respectively, and ε_1 and ε_2 denote the proportional and additive errors, respectively, with the residual variance conforming to a normal distribution with a mean of 0 and variance of σ^2.

The candidate covariates were selected using a forward incorporation approach to build the final sertraline PPK model. In the forward incorporation stage, all covariates were added to the base model one by one. When a covariate's addition caused the objective function value (OFV) to drop by more than 6.63 ($P < 0.01$, $df = 1$), it was deemed to be kept in the model. For continuous variables such as age, height, weight, and BMI covariates were represented by Eq. (3), while for discontinuous variables such as gender and combined medication use were represented by Eq. (4).

$$P_i = \widehat{P} \times e^{\eta_i} \times [1 + \theta_{COV} \times (COV - \overline{COV})] \tag{3}$$

$$P_i = \widehat{P} \times (1 + \theta_{COV} \times COV) \tag{4}$$

Where COV_i and $\overline{COV}$ denote the covariate value of the i individual and the median value of the covariate, respectively. For gender covariates, COV of 0 and 1 represent males and females, respectively. For the covariate of combination medication, 0 and 1 represent not receiving combination therapy and receiving combination therapy during treatment with sertraline, respectively.

2.4. Model evaluation

The ability of the final covariate model and the precision of the parameters were assessed by NPDE, goodness-of-fit plots, and bootstrap. The NPDE is a method for evaluating the model based on the fit of each observation in a way that is not easily influenced by the experimental design. Goodness-of-fit plots were used to assess the quality of the final model, such as the ratio of population-observed concentration values to predicted values, individual concentration observations to predicted values, and population predicted concentration values to conditionally weighted residuals (CWRES) at the time of dosing. Bootstrap was used to resample 1000 times for analysis and the median values, and 95 % confidence intervals of the resulting results were compared with the corresponding parameters of the original data.

2.5. Model simulation

We simulated serum drug concentrations in teenagers at various doses in order to derive mean serum drug concentrations from the literature cited by the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP) guidelines. Additionally simulated were teenagers' discontinuation plans for once-daily (QD) and twice-daily (BID) treatment regimens at various levels. The seven regimens for cessation were as follows: 1) Reduce the dose by 25 mg every 3 days; 2) reduce the dose by 25 mg every 7 days; 3) reduce the dose by 25 mg every 14 days; 4) reduce the dose by 50 mg every 3 days; 5) reduce the dose by 50 mg every 7 days; 6) reduce

Table 1
Demographic data of patients.

Characteristic	N	Median (Range)	Mean (SD)
Number of patients	140	–	–
Concentration data (ng/ml)	298	–	–
Gender (M/F)	70/70	–	–
Age (years)	–	22 (11,79)	27.46 (16.43)
<18	52	–	–
18–65	75	–	–
>65	13	–	–
Weight (kg)	–	60 (40–110)	61.54 (14.58)
Height (cm)	–	166 (145,185)	165.46 (7.98)
BMI	–	36 (25–62)	37 (7.92)
Lamotrigine	99 (33.22 %)	–	–
Quetiapine	12 (4.03 %)	–	–
Venlafaxine	4 (1.34 %)	–	–

the dose by 1/2 of the original amount every 3 days, followed by a maintenance of 1/2 of the remaining amount for 7 days; 7) reduce the dose to 1/2 of the original amount every 7 days, followed by 1/2 of the remaining amount for 7 days.

In the AGNP guidelines, the recommended therapeutic drug concentration reference range for sertraline is 10–150 ng/mL [21]. And there is no guideline reference for adolescent patients. Based on the final model, the rational dosing and rational withdrawal of adolescents were simulated to provide a reference for the rational dosing and safe withdrawal of adolescent patients.

3. Results

3.1. Demographic data

A total of 140 patients with psychiatric disorders (70 males and 70 females) and 298 therapeutic drug monitoring (TDM) outcomes at trough concentrations were included in the PPK model of sertraline. Demographic details (e.g., age, gender, weight, height, BMI, and comorbid medications) of the enrolled patients are shown in Table 1.

3.2. Model development

The best suitable model to describe the pharmacokinetics of sertraline is a one-compartment model of absorption and elimination. We fixed the summation error to 0 and used a proportional type error model to describe the present model. The OFV value of the base model was 2356.936 and the estimated relative standard error parameters of the base model were CL/F of 7 % and V/F of 26 %. The intraindividual variability in the proportional error model was 0.001. The main results of the covariate analysis are described in detail in this paper. The OFV of the model decreased by 7.081 ($P < 0.01$) by adding the age covariate to the forward inclusion process, thus age may be an important covariate for sertraline CL/F. Gender, height, weight, BMI, and combined medications were not found to have a significant effect on the decrease in OFV values during the inclusion process. Thus, we developed the final model of age for CL/F and described the PK parameter estimates of the final model in detail in Table 2. The following equation was used to define the final PPK model:

$$CL/F = 76.1 \times [1 - 0.0068 \times (AGE - 22)]$$

$$V/F = 803$$

$$K_a = 0.098$$

3.3. Model evaluation

Model diagnostic plots, also known as goodness-of-fit plots, are used to evaluate the quality assessment of the final model, which assesses not only the precision of parameters and the reasonableness of relative standard errors but also the variability of inter- and intra-individual variability. Four scatter plots, including population predicted concentration versus observed concentration (Fig. 1A), individual predicted concentration versus observed concentration (Fig. 1B), conditional weighted residual versus individual predicted concentration (Fig. 1C), and conditional weighted residual versus time after last dose (Fig. 1D), are included in Fig. 1. Based on the observations in Fig. 1, a good linear relationship was found between the population and individual predicted values and the observed values, indicating a good fit for the model. The NPDE was used to evaluate the validity of the PPK model for sertraline. The results showed that the PPK model had strong predictive power, as evidenced by the quantile-quantile plots (Fig. 2A), the NPDE distribution histogram (Fig. 2B), the plot of NPDE vs time (Fig. 2C), and the NPDE versus predicted concentration (Fig. 2D). Bootstrap was used to obtain the cumulative distribution of sertraline by resampling simulations for each observation 1000 times. The median value of the parameter estimates from the final model with the bootstrap results is presented in Table 2, along with their standard errors and 95 % confidence intervals. All parameter estimates from the final model were within the 95 % confidence interval, indicating the good stability of the model constructed by this sertraline.

3.4. Model simulation of blood drug concentrations in adolescents

The results of the analysis of covariates showed that age was a significant covariate affecting the clearance of sertraline. The

Table 2
Population pharmacokinetic final model parameters and bootstrap results for sertraline.

Parameter	Final Model			Bootstrap	
	Estimate	RSE (%)	IIV (CV%)	M	95 %CI
CL/F	76.1	7	10	74.68	67.22–87.71
V/F	803	26	57	809.443	372.19–1369.47
K	0.098 FIX	–	–	0.098 FIX	–
θ_{CL-AGE}	0.0068	24	–	0.0063	0.004–0.0104
PRO (CV%)	0.129	12	–	0.128	0.088–0.166

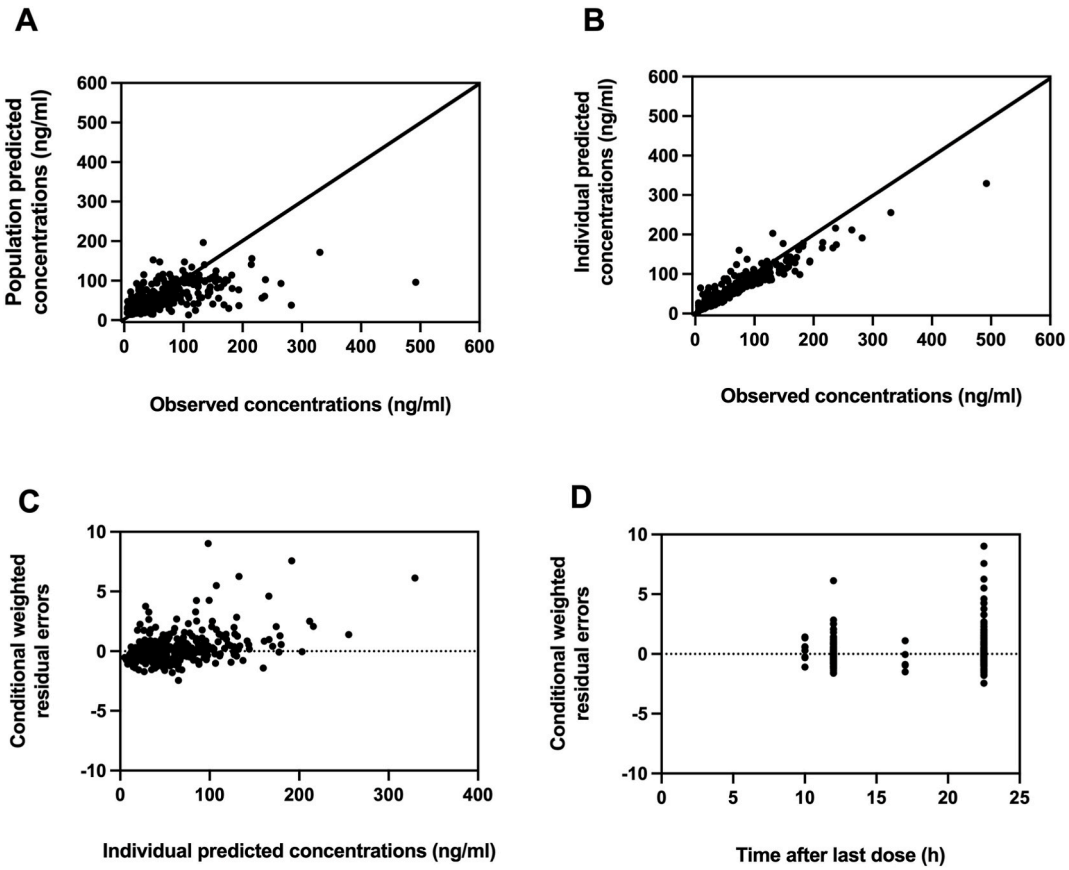

Fig. 1. Plots showing the final population PK model's goodness-of-fit for the chosen sertraline concentration. (A) Population predicted concentrations vs. observed concentrations; individual predicted concentrations versus observed concentrations are shown in (B); individual predicted concentrations versus conditional weighted residual errors are shown in (C). Time after last dose and conditional weighted residual errors in (D).

fluctuation of serum concentration in the two populations at different doses was simulated using 15-year-old adolescents and 45-year-old adults as mean age representatives. The AGNP guidelines state that the reference therapeutic concentration range for sertraline in adult patients is 10–150 ng/ml, with a laboratory threshold concentration of 300 ng/ml. In Fig. 3, we found that both adults and adolescents can reach the therapeutic range specified by the guidelines at doses of 25–250 mg. In addition, the serum drug concentration in adolescents was lower than in adults due to faster clearance, but there was no significant difference.

The referenced literature was developed according to the reference range of therapeutic drug concentrations in the AGNP guidelines [22,23], and it was found that the mean serum drug concentrations in the referenced literature on adolescents varied considerably, with 2.08 and 3.02, respectively, corrected for dose-concentration ratios, whereas the mean serum drug concentration in adults was 67 ng/ml [24], and thus we used the final model to simulate the serum drug concentrations in adolescents at serum drug concentrations at different doses. As shown in Fig. 4, at daily doses of 25–250 mg, adolescent patients were able to meet the sertraline therapeutic window range for adults. In addition, adolescents were able to achieve the average adult concentrations in the guideline literature at a dose of approximately 150 mg.

3.5. Model simulation of rational drug withdrawal in adolescents

The patients in this study were administered mainly QD and BID. Under the QD dosing regimen, we simulated the fluctuation of plasma drug concentration of patients with different strategies at doses of 50 mg (Fig. 5A), 100 mg (Fig. 5B), 150 mg (Fig. 5C) and 200 mg (Fig. 5D) respectively, and the results showed: direct discontinuation resulted in too rapid a decrease in serum concentrations. At low doses of 50 mg and 100 mg, time had less effect on fluctuations in serum concentration, and regimen 1 was able to reach a steady state while declining rapidly over a short period. At high doses of 150 mg and 200 mg, regimens 1, 2, and 3 all produced decreases in serum concentrations after reaching a steady state, but regimen 2 was more gradual and required less time than regimen 3 for the same time-reduced dose. Regimens 4–7 all produced rapid decreases in serum concentrations.

Under BID administration, we simulated various withdrawal strategies for 50 mg and 100 mg, and designed four scenarios of 50 mg starting in the morning (Fig. 6A) and starting in the evening (Fig. 6B), and 100 mg starting in the morning (Fig. 6C) and starting in the evening (Fig. 6D) according to the situation of taking one dose in the morning and one dose in the evening: the reductions were also

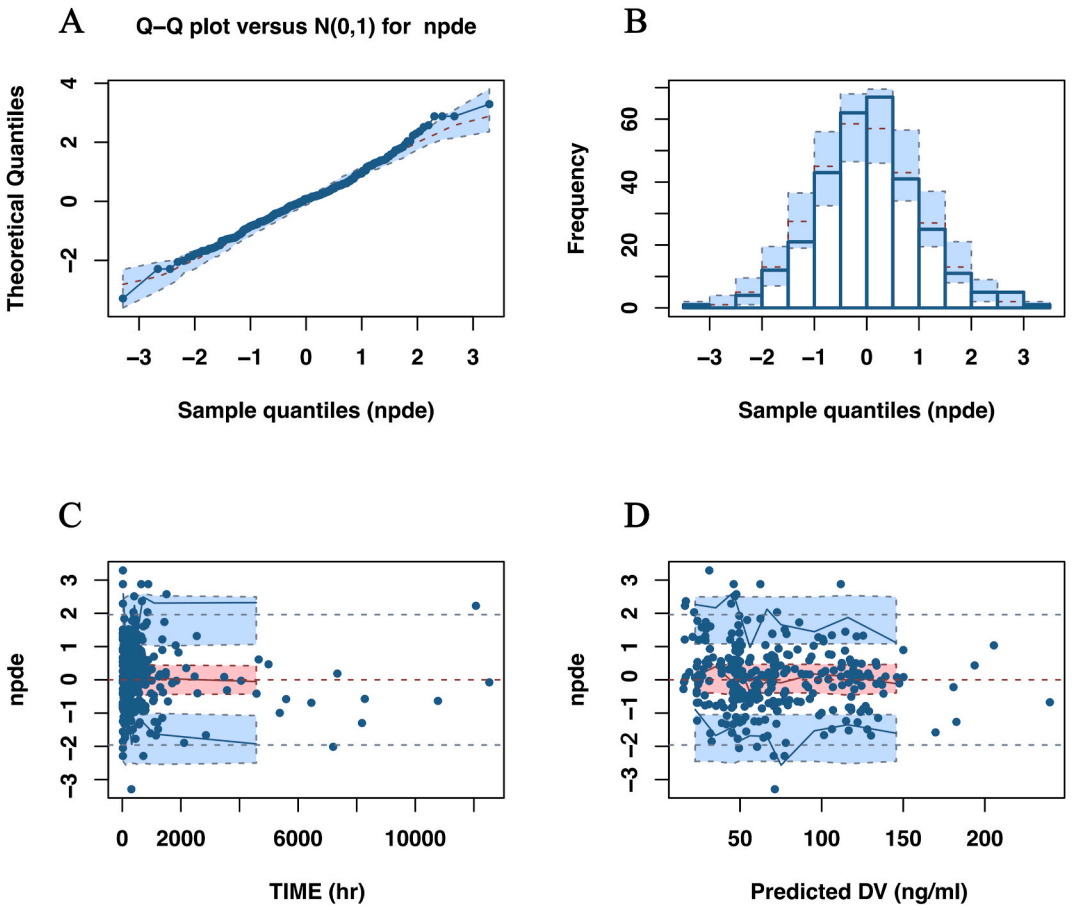

Fig. 2. The NPDE plots of the PPK model. (A) The quantile–quantile plot; (B) the distribution histogram of NPDE; (C) the NPDE versus time; (D) the NPDE versus predictions concentration.

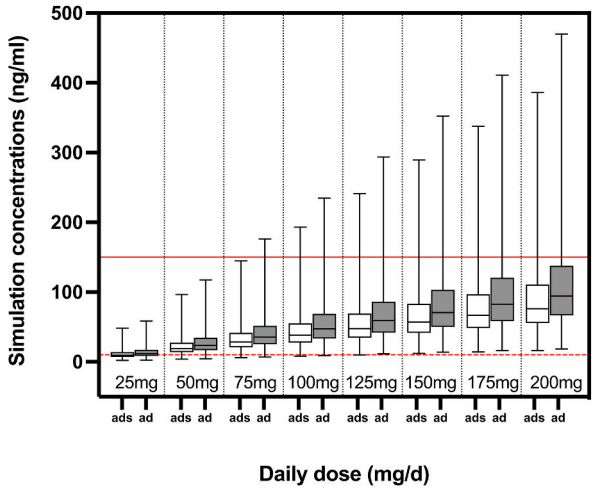

Fig. 3. Plots of fluctuating serum drug concentrations in adolescents and adults at different doses. The ads and ads represent adolescents and adults, respectively. The red dashed line and the red solid line represent the lower and upper limits of the therapeutic window, respectively. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

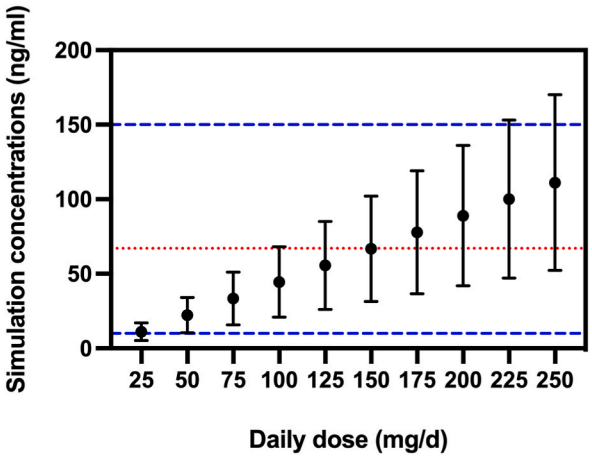

Fig. 4. Plot of fluctuating serum drug concentrations in adolescents at different doses. The red dashed line represents the range of the therapeutic window, and the blue dashed line represents the average concentration in adults. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

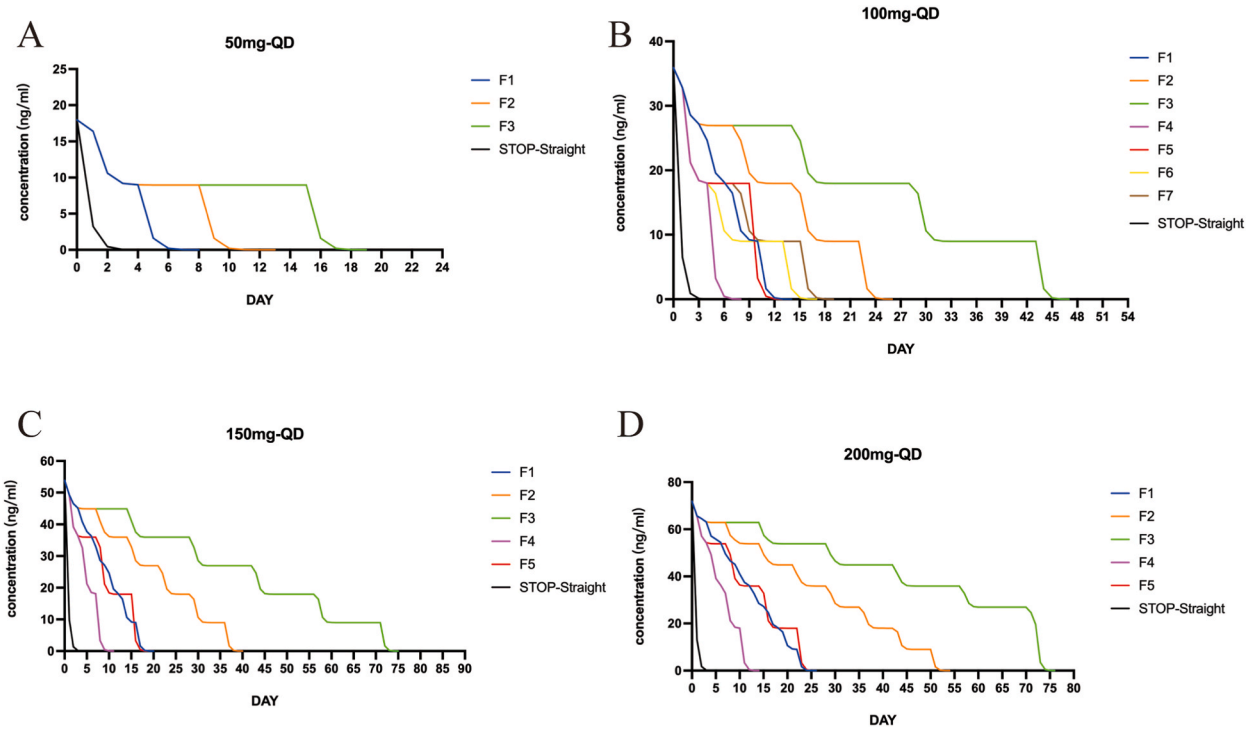

Fig. 5. Steady-state serum concentration plots for adolescent patients under simulated QD administration scenarios. A) Plots of plasma drug concentration fluctuations in patients with different discontinuation regiments and direct discontinuation at 50 mg. B) Graph of plasma concentration fluctuation of patients with different discontinuation strategies and direct discontinuation at 100 mg. C) Plots of plasma concentration fluctuation of patients with different discontinuation strategies and direct discontinuation at 150 mg. D) is the plasma concentration fluctuation chart of patients with different discontinuation strategies and direct discontinuation at 200 mg.

equal, split between reductions from the morning first and from the evening first. Direct discontinuation serum concentration levels decreased rapidly within a short period. The timing of the commencement of the decreases had minimal impact on these variations, and at the 50 mg lowering the dose, changes in serum concentrations in the evening and morning followed a similar pattern. After achieving a steady state, serum concentrations in regimens 1, 2, and 3 were all able to stable decrease, and regimen 1 was able to complete cessation in a shorter amount of time. At 100 mg, regimens 1, 4, and 5 tended to decline too quickly, but regimens 2 and 3 fluctuated the serum concentration more gradually at the same lowered dose, with regimen 2 having a longer time to discontinue than

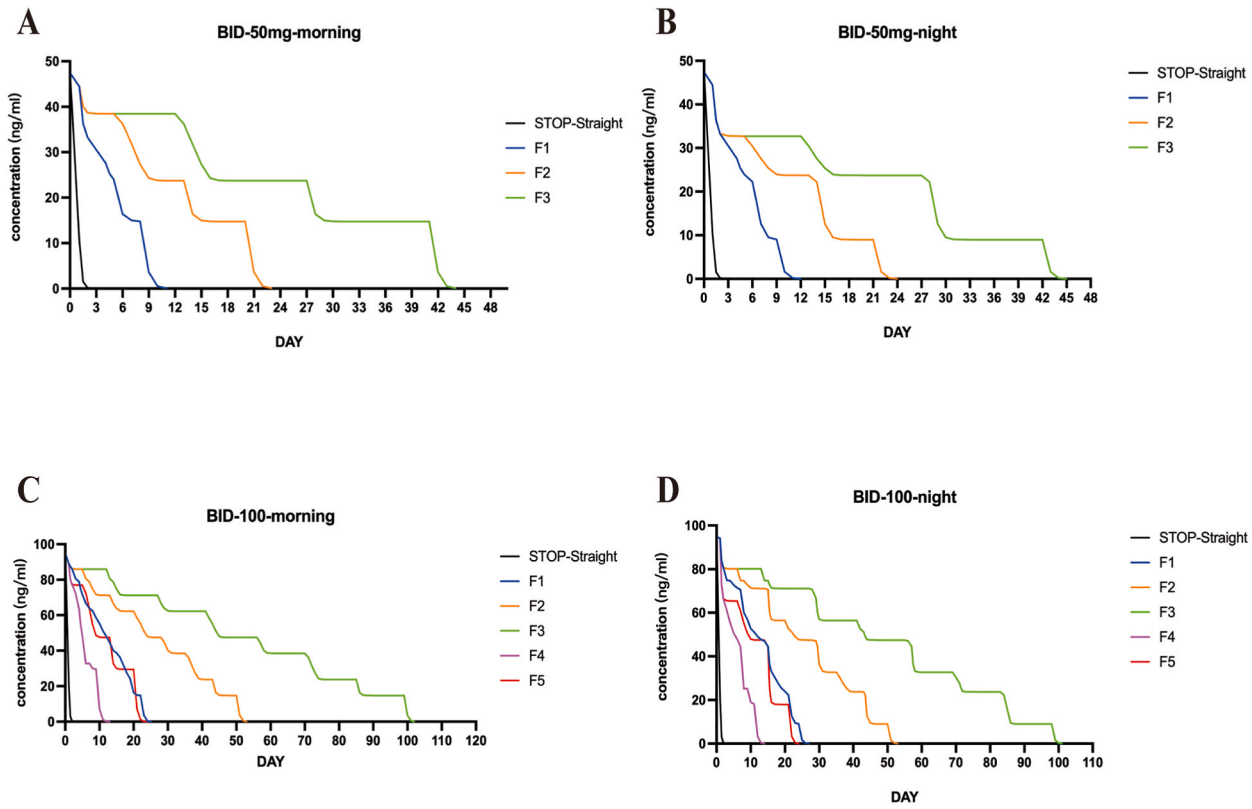

Fig. 6. Steady-state serum concentrations in adolescent patients under simulated BID administration are plotted. A) Plots of plasma concentration fluctuations in patients with different regiments of morning discontinuation and direct discontinuation at 50 mg. B) Plots of plasma concentration fluctuations in patients with different strategies for discontinuation at 50 mg starting at night versus direct discontinuation. C) Plots of plasma concentration fluctuations in patients with different strategies for discontinuation at 100 mg starting in the morning versus direct discontinuation. D) Plots of plasma concentration fluctuations in patients with different strategies for discontinuation at 100 mg starting at night versus direct discontinuation.

regimen 3.

4. Discussion

To our knowledge, this is the first PPK study of sertraline in Chinese patients with mental disorders. First, we developed a single-compartment model to describe the pharmacokinetic parameters and demonstrated the accuracy of the model in predicting sertraline serum concentrations by model validation. In addition, we explored the effects of different factors on sertraline pharmacokinetics by PPK modeling. Based on the TDM data and PPK model, we also provide suggestions and references for rational drug administration and safe withdrawal of sertraline in adolescents.

Based on our study of sertraline, we found that the mean dose-adjusted serum drug concentration (concentration/daily dose) was consistent with the AGNP guidelines, suggesting that pharmacokinetic differences between races are minimal. In a PPK study of sertraline, sertraline concentration data from 53 patients were used to find that N-desmethyl sertraline was a covariate affecting sertraline clearance [25]. In another, PPK study on sertraline and escitalopram, the CYP2C19 genotype was found to be a potential factor affecting sertraline clearance [26]. In this study, we used $P < 0.01$ as a criterion for screening covariates, and the only covariate that was finally screened was age, and sertraline clearance in patients decreased with increasing age. However, we did not find an effect of other factors (including weight, height, body mass index, and coadministration) on the pharmacokinetics of sertraline. Due to the lack of data on N-desmethyl sertraline concentrations and CYP2C19 genotypes in the patient portion of this inclusion, they were not included as covariates in the study. Sertraline is metabolized in the liver by CYP metabolizing enzymes, but liver function and its related indexes were not examined in this study. Clinical studies have shown that sertraline is almost unaffected by complete hepatic and renal function at routine doses, and patients with hepatic insufficiency or impaired hepatic function need to reduce the dose appropriately and pay attention to fluctuations in serum concentration. The major metabolizing enzymes of sertraline are CYP2B6 and CYP2C19. The initial inclusion of CYP2C19 as a covariate in this study did not result in an effect on clearance, and we speculate that this may be due to the small sample size of the study ($n = 38$), which affected the results of the effect of CYP2C19 on sertraline and is therefore not shown in this text. The metabolic phenotype of CYP2C19 does not differ significantly between ethnic groups [27,28].

Studies have shown that sertraline exposure in patients with ultra-rapid metabolizers (UM) of CYP2C19 is approximately 20 % less than in patients with poor metabolizers (PM) compared to controls, while PM patients with both CYP2C19 and CYP2B6 have 189 % higher sertraline concentrations [29]. It is possible that it is not a polymorphism in a single metabolizing enzyme gene that affects sertraline pharmacokinetics, but more likely a combination of multiple metabolizing enzyme genes [30,31]. The focus of this study is how other psychiatric agents affect the distribution of sertraline clearance or apparent volume. Many drug interactions in clinical practice are not only related to therapeutic agents for psychiatric and neurological disorders. Proton pump inhibitors (PPIs) may decrease sertraline metabolism by blocking CYP2C19, which would increase serum drug concentrations, according to a study on the serum concentrations of SSRIs [32]. Furthermore, some herbal or botanical preparations have pharmacokinetic and pharmacodynamic interactions with SSRIs, and the risk of adverse reactions associated with them also deserves our attention [33]. According to the findings of a PK modeling study conducted on depressed teenagers, teens who have access to cannabidiol (CBD) may be more susceptible to negative effects because of inhibition of CYP2C19 metabolism, which raises the body's content of sertraline [34].

Long-term use of SSRI analogs is associated with antidepressant discontinuation syndrome (ADDS) in approximately 30–50 % of patients after abrupt discontinuation [35]. Although physician awareness of antidepressants has increased, scientific education to guide patients on how to discontinue medications scientifically is still lacking [36]. There is no definitive way to prevent the onset of withdrawal symptoms, but tapering may be a more reasonable and safe clinical strategy for reducing ADDS in patients taking SSRIs, especially in the special population of adolescents aged 13–18 years. Currently, there are no clear instructions on how to discontinue sertraline. Most of the previously commercially used sertraline tablets were in the 50 mg/tablet size, so we designed protocols regarding adolescent discontinuation using half a tablet (25 mg) and one tablet (50 mg) as reduced dose regimens1-5. In addition, we have designed a common dose reduction regimen 6–7 based on clinicians' clinical experience of reducing the dose to 1/2 of the original tablet and maintaining it at the remaining 1/2 for 7 days. Based on the simulation results, we suggest that the low dose of 50 mg and the medium dose of 100 mg can be preferentially reduced at 3- or 7-day intervals with a fixed dose of 25 mg in QD. At high doses of 150–200 mg, the serum concentration decreases too rapidly in fixed dose decreases of 50 mg. The decreasing trend of serum concentration in fixed-dose decreases of 25 mg is similar, but the decreasing trend is too rapid in the decreasing regimen with a 3-day interval, so a 25 mg decreasing regimen with a 7- or 14-day interval is recommended. For BID dosing, whether 50 mg or 100 mg, we believe that tapering at 7- and 14-day intervals with a fixed dose of 25 mg appears to be a more prudent regimen. We found that a regimen of reducing the dose to 1/2 of the original dose at various time intervals and maintaining the remaining 1/2 of the dose for 3 or 7 days was not superior to a fixed dose reduction regimen. In addition, we examined dose reduction options of 1/3 and 1/4 reduction but did not adopt them in consideration of the specific practicalities of the patients themselves and the healthcare providers, and the size of the tablets. At doses of 50–200 mg, the required discontinuation time needs to be extended with increasing doses at discontinuation. The different dosing regimens have little effect on serum concentration fluctuations on discontinuation, and the difference in serum concentration fluctuations and decreasing trends for the BID dosing regimen whether the dose is reduced first in the morning or the evening is also less pronounced. Therefore, we advise that in addition to evaluating the length of treatment maintenance, it's also crucial to pay attention to changes in serum concentrations and patient-specific symptoms while making dose modifications. The larger the dose of medication taken, the longer the withdrawal time required.

The two published PPK studies on sertraline had values of 0.373 and 0.029, respectively, regarding the pharmacokinetic parameter CL/V, which is inconsistent with the CL/V value of 0.095 in this study. Being that the mean doses in the two articles and in this study were almost identical, we speculate that the difference in CL/V may be a result of other factors. The first is the population, in both articles, one studied a Serbian population and the other a mixed European population with possible metabolic differences from the Asian Chinese population of the present study. Second is the age distribution, with adolescents comprising 1/3 of the population and a mean age of 22 in this study, compared to 56 and 14 in the two studies. Sertraline is not currently approved for the treatment of depression in children and adolescents, and numerous studies have examined the safety and efficacy of sertraline in this age group by examining the incidence of adverse effects and related scale scores in children and adolescents aged 6–18 years at 50–200 mg. However, there are no guidelines for dosing and effective therapeutic concentration reference ranges for sertraline in children and adolescents. Related studies have shown no significant differences in metabolic half-life and metabolite concentrations between adults and adolescents when sertraline is administered orally at the same dose, concluding that sertraline can be used at standard adult doses for the treatment of depression or OCD in adolescent patients [17]. Axelson and his colleagues suggest that the vast majority of adolescents benefit from an initial dose of 50 mg, and he also indicates that adolescents are more likely to benefit from a twice-a-day dosing frequency [8]. Therefore, in clinical practice, the dose of drugs for adolescents is generally extrapolated from the dose and therapeutic concentration reference range of adults to carry out therapeutic drug monitoring and individualized treatment. This extrapolation approach ignores to some extent the differences in pharmacokinetics and pharmacodynamics between adolescents and adults. It was learned through simulation that serum drug concentrations were within the therapeutic window in almost all patients. Neither adolescent nor adult patients exceeded the upper limit of the reference range for therapeutic concentrations (150 ng/mL) when dosed at 25–250 mg daily. Adolescents, on the other hand, can achieve the average adult dose of 150 mg and be within the reference range of therapeutic concentrations. In addition to the literature cited in the guideline, we found other studies of serum concentration levels of sertraline in adolescents (51.39) to be consistent with the mean concentration in this study (64.39) [23,37].

We fully recognize that this study has some minor flaws. First, this was a retrospective study analyzing TDM data. Second, we did not examine the effects of genotype and N-desmethyl sertraline on sertraline serum drug concentrations, which we will try to investigate by expanding the sample size in subsequent studies. Third, the measured serum drug concentration and the target site have some differences, and the serum drug concentration can only reflect the process of drug changes in the patient's body and cannot specifically correspond to the specific efficacy and adverse effects. Despite these shortcomings, our PPK model study of sertraline in Chinese patients can provide a reference for the rational use of drugs in Chinese patients, and the results of the model can be used to

help optimize the dosing regimen and provide a reference for the safe withdrawal of drugs in adolescent patients.

5. Conclusion

In summary, we developed the first population pharmacokinetic model for sertraline in Chinese patients with mental disorders and identified age as an important covariate affecting sertraline clearance, and the model was able to predict sertraline concentrations well in Chinese patients with mental disorders. In addition, this model not only helps to develop individual treatment plans for patients but also the results of the model simulation provide a safe discontinuation plan for adolescent patients who need to withdraw sertraline.

Ethics approval and informed consent

The study protocol was approved by the Institutional Review Board (IRB) of the Affiliated Brain Hospital of Guangzhou Medical University (approval number: 2021027). This study is retrospective and does not involve patient privacy, and informed consent is not required to be signed by patients after approval by the ethics committee.

Data availability statement

The research-related data is not stored in publicly available repositories. Data will be made available on request.

CRediT authorship contribution statement

Zi Zhang: Writing – review & editing, Writing – original draft, Validation, Investigation, Formal analysis, Data curation. **Zhihao Guo:** Writing – original draft, Investigation, Data curation. **Yaqian Tan:** Validation, Software, Funding acquisition. **Lu Li:** Software, Methodology, Funding acquisition. **Zhanzhang Wang:** Software, Resources, Funding acquisition. **Yuguan Wen:** Visualization, Resources, Project administration, Conceptualization. **Shanqing Huang:** Visualization, Supervision, Resources, Project administration, Conceptualization. **Dewei Shang:** Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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