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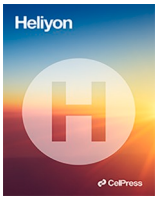

Research article

A 6-year retrospective study of olanzapine plasma concentration inpatients with schizophrenia CYP1A2 polymorphisms in real-life settings☆

Yan Zhang [a,b], Lisha Sun [a,b,1], Yanli Su [a,b,*], Hui Wang [a,b]

[a] Xi'an Mental Health Center, 710100, Xi'an, Shaanxi, PR China
[b] Xi'an Key Laboratory of Pharmacy (Mental Health), 710100, Xi'an, Shaanxi, PR China

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ABSTRACT

Aim: to investigate the potential influence of CYP1A2 polymorphisms on olanzapine plasma concentration of inpatients with schizophrenia in real-life settings.
Methods: 409 inpatients who received OLA for at least 2 weeks, from June 2016 to March 2022 were included in the retrospective investigation. Moreover, 503 samples of above inpatients receiving OLA was built to investigate the influence of the relevant OLA plasma concentration, polymorphisms CYP1A2 -163C/A on the inpatients outcome.
Results: Scale score reduction rate (SSRR) in 1 mutated CYP1A2 -163C/A alleles (CA) was significantly higher than other CYP1A2 alleles (CC + AA) ($P = 0.002$). Inverse S-curve correlations relationship was between SSRR and plasma concentrations of OLA ($r = 0.130$, $P < 0.005$). When remove ineffective subjects (ineffective group), the results of all CYP1A2 -163C/A genotype showed perfect correlations relationship tendencies with SSRR ($r = 1.000$). The best concentrations of OLA corrected for daily dose (C/D) range and the best concentration range of OLA of all CYP1A2 -163C/A genotype was 3.18–3.53 ng/mL/mg and 17.42–57.33 ng/mL. The C/D range and concentration range of OLA were 2.722–4.221 ng/mL/mg and 13.61–84.42 ng/mL, which belong CYP1A2 -163C/A CA genotype subjects, was largest.
Conclusions: The best effective C/D range and concentration range of OLA respective were 3.18–3.53 ng/mL/mg and 17.42–57.33 ng/mL, which range values of CYP1A2 -163C/A CA genotype of inpatients with schizophrenia was largest.

1. Introduction

Schizophrenia is the most common and difficult to treat type of mental disorder. At present, olanzapine (OLA) is one of the most frequently used drugs in clinical treatment of schizophrenia [1,2]. In the observation of clinical use, Olanzapine has problems such as individual differences in patients, multiple targets leading to many adverse reactions, and the half-life of Olanzapine in different patients may differ by more than 30 h at most [3–5].

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* Corresponding author. East section of Hangtian Avenue, Xi'an, 710100, PR China.
E-mail address: zy22661685@163.com (Y. Su).

[1] Lisha Sun contributed equally to this work.

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UGT1A4, the cytochrome P450 (CYP) 1A2, 2D6 and the flavin-containing monooxygenase were metabolic enzymes of OLA. CYP1A2*1F polymorphism (−163C.A, rs762551) has been implicated as the most relevant factor to OLA plasma concentration [6–9], CYP2D6 only plays a minor role [10]. The genetic analysis data of our research group from 2016 to 2022 proved the existence of this difference in the population in the northwest of China. The research results showed that the CYP1A2 of the population had an ultra-fast metabolism of nearly 40 %, normal metabolism>50 %, and about 10 % intermediate metabolism. In general, OLA metabolites are less active than the parent compound so that consideration of metabolite concentrations is not warranted in the context of TDM [11]. Variables as sex, age, body weight, and dose explains only 24 % of the variance in OLA plasma concentration [12–15]. Therefore, mainly studied effect of CYP1A2 polymorphism on rang of OLA concentration and efficacy in this study. Moreover, the potential influence of sex, age, and baseline weight was addressed.

2. Materials and methods

Inpatients were collected from June 2016 to March 2022 in real-life settings at the psychiatric department at Xi'an mental health center, Shaanxi, China. 409 inpatients who received OLA at least 2 weeks as a part of their clinical treatment for were included in our investigation. The study population had been analyzed regarding CYP1A2 -163C/A (rs762551) polymorphisms. The study population (=plasma cohort) consisted of 409 inpatients, of which 76 received monotherapy with OLA as the only antipsychotic drug. A total of 33 patients received a combination treatment with both second-generation and first-generation (mainly pipamperone and haloperidol, both n = 8) antipsychotic drugs. 119 patients received an additional atypical co-medication [risperidone (n = 36), quetiapine (n = 5), paliperidone and amisulpride (n = 1), clozapine (n = 17), amisulpride (n = 31), aripiprazole(n = 40) and ziprasidone (n = 20)], and 1 patients received carbamazepine as CYP1A2 influencing co-medication.

The design of the study was open. The inclusion criteria were psychotic conditions [International Classification of Disease-10 (ICD-10): F2: schizophrenia, schizotypal, and paranoid disorder] that necessitate treatment with second-generation antipsychotics. Patients younger than 18, patients suffering from organic disorders (ICD-10: F0), or drug addicts (ICD-10: F1) were excluded from the study. Further exclusion criteria were breast-feeding or pregnancy. No patients admitted to the hospital by law or authority direction were included in the study. The study was approved by the Ethics Committee of Xi'an Mental Health Center (XAJWKY-201801).

2.1. Plasma concentrations

Patient samples were collected at psychiatric department at Xi'an mental health center, directly send to pharmaceutical laboratory centrifuged, and measured as soon as possible. Samples were stored refrigerated at −80C. Steady-state plasma samples (after at least 1 week at a fixed OLA dose, 10–12 h after dose in >2 weeks of OLA treatment) were available for 409 patients and were measured by tandem mass spectrometry (LC–MS/MS) [16]. Main modifications were the use of different instruments (Hunan Demeter MS-Mate 9500 in combination with Shimadzu 8050) and different HPLC Column (MSCB C18 column, 3.0 mm × 50 mm, 3.3 μm; Hunan Demeter Instruments, Hunan, China). The lower limit of quantification was 2.65 ng/mL. With commercial control samples (Hunan Demeter Instruments, Hunan, China) containing 24.14, 48.27 and 120.68 ng/mL OLA, the recovery was 100 ± 6.8 %. Control values were validated during 90 days of measurement, and a total number of 180 runs were used for validation. Within the calibration range, typical average coefficients of variation were 4.5 % for intra-assay and 5.3 % for interassay comparisons, whereas average deviations from spiked concentrations ranged from 2.9 % to 4.8 %.

2.2. Genotyping

We examined 409 blood samples obtained from inpatient subjects giving informed consent on the genetic analysis of their DNA. The ethylenediamine tetra-acetic acid (EDTA)-supplemented blood was extracted with the magnetic bead method DNA Purification Kit (Xi'an Tianlong Technology Co., Ltd, China) according to the manufacturer's instructions. DNA was stored at 4 °C or frozen at −20 °C for long-term storage. Preparation of DNA and genotyping of the CYP1A*1F was performed as described elsewhere [17] on the Step One Plus (Thermo Fisher Scientific, Life Technologies Holdings Pte Ltd, Singapore). For more detailed information, refer Table 1.

Table 1
Monoplex Hybridization-Probe Method for CYP1A*1F rs762551.

Primer/Probe	Modification	Sequence	Conc. [nM]
Temperature program: 95 °C, 600 s; 35✖ (95 °C, 10 s; 57 °C, 10 s; 72 °C, 20 s); 43 °C-73 °C at 0.1 °C/s.			
CYP1A2*1F F-Primer		GTCACTTGCCTCTACTCCAGC	375
CYP1A2*1F R-Primer		CTGATGCGTGTTCTGTGCTTG	375
CYP1A2*1F sen	3' -Fluorescein	GGGCCCAGGACGCAT	100
CYP1A2*1F anc	5′ LCRed640 3' -Phosphate	GTAGATGGAGCTTAGTCTTTCTGGTATCCA	100

The mutation site is underlined.

2.3. OLA efficacy evaluation

The 30-item positive and negative syndrome scale (PANSS) was conceived as an operationalized, drug-sensitive tool that provides clinical assessment of schizophrenia treatment of OLA [18]. The primary measure of efficacy was the PANSS total score reduction rate. Scale (PANSS) score reduction rate (SSRR) of 503 inpatient samples when collecting, compared with on admission was calculation. Therefore, in the calculation, the item base score of 30 points is subtracted from the denominator. Unified criteria for judging the OLA efficacy, if SSRR less than 25 %, the treatment is ineffective, if SSRR equal or more than 25 % is effective (25 %–49 % is improved, 50 %–74 % is significant progress, ≥75 % is basically cured). Hence, OLA efficacy was divided into 4 levels. According to the 4 levels of curative effect, the corresponding plasma concentrations of OLA, C/D, C/D/BW were divided into 4 groups.

2.4. Statistics

The doses of OLA administered, the plasma concentrations of OLA (corrected for dose and body weight), and the concentrations of OLA corrected for daily dose (C/D) among subjects with different numbers of mutated alleles (CYP1A2*1F) were compared using the Kruskal-Wallis test. The Kolmogorov–Smirnov test was used to assess the normality of data distribution. The ×2 and Kruskal-Wallis tests and one-way analysis of variance were performed for comparisons of sex, age, and body weight among genotypes. Stepwise multiple regression analysis was performed to analyze the relationship between independent variables (sex, age, and number of mutated alleles [CYP1A2*1F]) and subject-dependent variables (plasma concentrations of OLA [all corrected for dose and body weight]). Dummy variables were assigned for sex (men = 0 and women = 1) and smoking habit (nonsmoker = 0 and smoker = 1) as independent variables. All statistical tests were 2-tailed, and P values < 0.05 were considered significant. Statistical analyses were performed using Excel and GraphPad Prism version 8.4 (GraphPad Software, San Diego, CA).

3. Results

Significant positive correlations was observed between the daily dose of OLA (corrected for body weight) and plasma concentrations of OLA ($r = 0.348$, $P < 0.001$, Fig. 1).

Range of plasma levels of OLA (corrected for dose, dose and body weight), and SSRR seemed to spindle shape increase with an increase in the number of CYP1A2-mutated alleles (Table 2); C/D, C/D/BW and SSRR in subjects with 1 mutated CYP1A2 alleles were higher than that of subjects with 0 or 2 mutated CYP1A2 alleles. However, the increase of C/D and C/D/BW did not achieve significance ($P = 0.636$ and 0.522, Kruskal-Wallis test, Table 2), SSRR achieve significance ($P = 0.002$, Kruskal-Wallis test, Table 2). SSRR in subjects with 1 mutated CYP1A2 alleles was significantly higher than that of subjects with 2 mutated CYP1A2 alleles ($P = 0.002$, Dunn's multiple comparisons test, Fig. 2).

In addition, Combined Medication (CM, no/yes) and patients with adverse reactions (ADR no/yes) did not differ between the 3 groups ($P = 0.295$ and 0.363, Kruskal-Wallis test, Table 2). The same tendencies were observed in plasma levels uncorrected for body weight.

In addition, multiple regression analysis indicated, the number of mutated alleles has a significant relationship with SSRR ($P = 0.041$, Table 3). Also a significant relationship existed between sex and OLA, C/D, C/D/BW, SSRR ($P = 0.038$, 0.000, 0.000, 0.007; Table 3). No relationship were observed with OLA, C/D, C/D/BW among the 3 genotypes, also between SSRR and C/D/BW (Tables 2 and 3).

Inverse S-curve correlations was observed between SSRR and plasma concentrations of OLA ($r = 0.130$, $P < 0.005$, Fig. 3A). Inverse

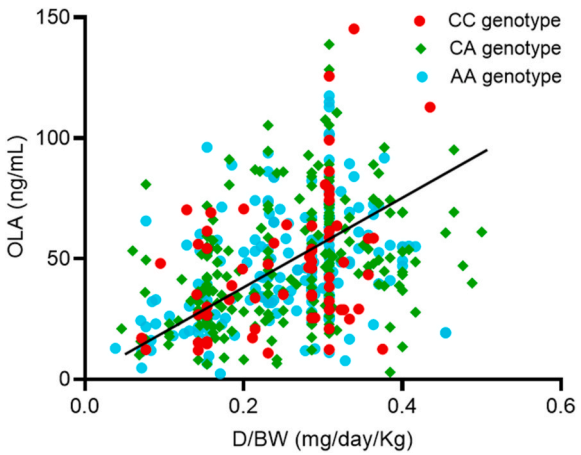

Fig. 1. Significant positive relationship between the daily dose of OLA (corrected for body weight) and plasma concentrations of OLA ($r = 0.348$, $P < 0.001$). Blank circles indicate patients with AA genotypes; blank squares indicate subjects with CC genotypes; and diamond indicate subjects with CA genotypes. Line indicate the regression lines.

Table 2
Relationship between the number of CYP1A2 mutated alleles (CYP1A2*1F) and corrected plasma levels of OLA (all corrected for dose and body weight) (n = 503).

Parameter	No. of CYP1A2-Mutated Alleles (CYP1A2*1F, −163C > A, genotype)			*P*
	0(CC genotype)	1(CA genotype)	2(AA genotype)	
Sex (male/female) *	24/44	101/134	78/122	0.613
Age (yr)[a]	31.50(14.00–59.00)	31.00(15.00–65.00)	32.00(15.00–70.00)	0.633
Body weight (kg)[b]	65.00(40.00–100.0)	65.00(40.00–108.0)	65.00(43.00–113.0)	0.698
Daily dose of OLA (D, mg/d)[b]	20.00(5.00–20.00)	20.00(5.00–20.00)	20.00(2.50–20.00)	0.418
Days of OLA Administered (d)[b]	29(6–63)	30(3–90)	28(2–93)	0.274
Daily dose of OLA corrected for body weight (D/BW, mg/d/kg body weight)[b]	0.286(0.071–0.434)	0.286(0.046–0.500)	0.286(0.038–0.455)	0.986
OLA(C, ng/mL)[b]	45.90(10.90–145.3)	45.00(3.00–138.8)	45.75(2.30–160.7)	0.799
C/D (ng/mL/mg)[b]	2.910(0.620–9.620)	2.990(0.150–16.16)	2.770(0.310–13.14)	0.636
C/D/BW (ng/mL/mg/kg)[b]	0.044(0.009–0.183)	0.047(0.003–0.249)	0.043(0.006–0.202)	0.522
Combined Medication (CM, no/yes) *	9/59	32/203	35/165	0.295
patients with adverse reactions (ADR no/yes) *	26/42	93/142	87/113	0.363
Scale score reduction rate (SSRR, %)[b]	33.57(0.00–85.71)	40.34(0.00–100.0)	31.98(0.00–100.0)	**0.002**

Data are expressed as the median (range).
*P value was calculated by the X^2 test.
ANOVA, analysis of variance; C/D, olanzapine corrected for dose; C/D/BW, olanzapine corrected for dose and body weight.
[a] Data are expressed as the median (range), and the P value was calculated by ANOVA.
[b] Data are expressed as the median (range), and the P value was calculated by the Kruskal-Wallis test.

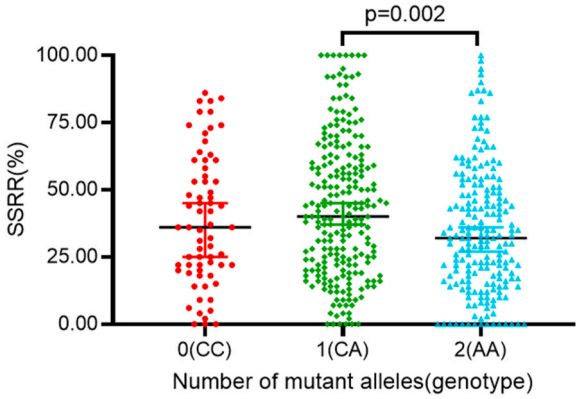

Fig. 2. Relationship between CYP1A2 genotype and SSRR. Horizontal bars show the median value of each group. Blank circles indicate patients with AA genotypes; blank squares indicate subjects with CC genotypes; and diamond indicate subjects with CA genotypes. Line indicate the regression lines. After the Kruskal–Wallis test, post hoc analysis was performed using the Dunn's multiple comparisons test.

Table 3
Results of multiple regression analysis.

Independent Variable	OLA (ng/mL)	C/D (ng/mL/mg)	C/D/BW (ng/mL/mg/kg)	SSRR (%)
Sex	0.002(0.038)	−0.248(0.000)	17.85(0.000)	0.221(0.007)
OLA				12.10(0.000)
C/D				0.193(0.027)
C/D/BW				–
Genotype(CYP1A2*1F)	–	–	–	−0.252(0.041)

S-curve were also observed between SSRR and C/D (Fig. 3B), SSRR and C/D/BW (Fig. 3C). The relationship of SSRR and C/D (Fig. 3B, grey line), SSRR and C/D/BW (Fig. 3C, grey line) are significant positively correlations (r = 1.000) When ineffective subjects (grey squares) removed.

To confirm the effect of CYP1A2*1F on OLA plasma concentration and treatment of schizophrenia, we analyzed the relationship of SSRR and C/D (daily dose included) among the 3 genotypes and 4 efficacy groups, but there were no rules (Fig. 3D). As shown in the figure, there is no unified trend in the changes of C/D values among the three genotypes. CC genotype show that basically cured group (the best therapeutic effect group) is corresponding to the lowest concentration of olanzapine. In the ineffective group of AA genotype, the concentration of olanzapine is be included in the concentration range of other responsive groups. The CA genotype shows that the group with the basically cured group and the ineffective group almost correspond to the same concentration range of olanzapine. The

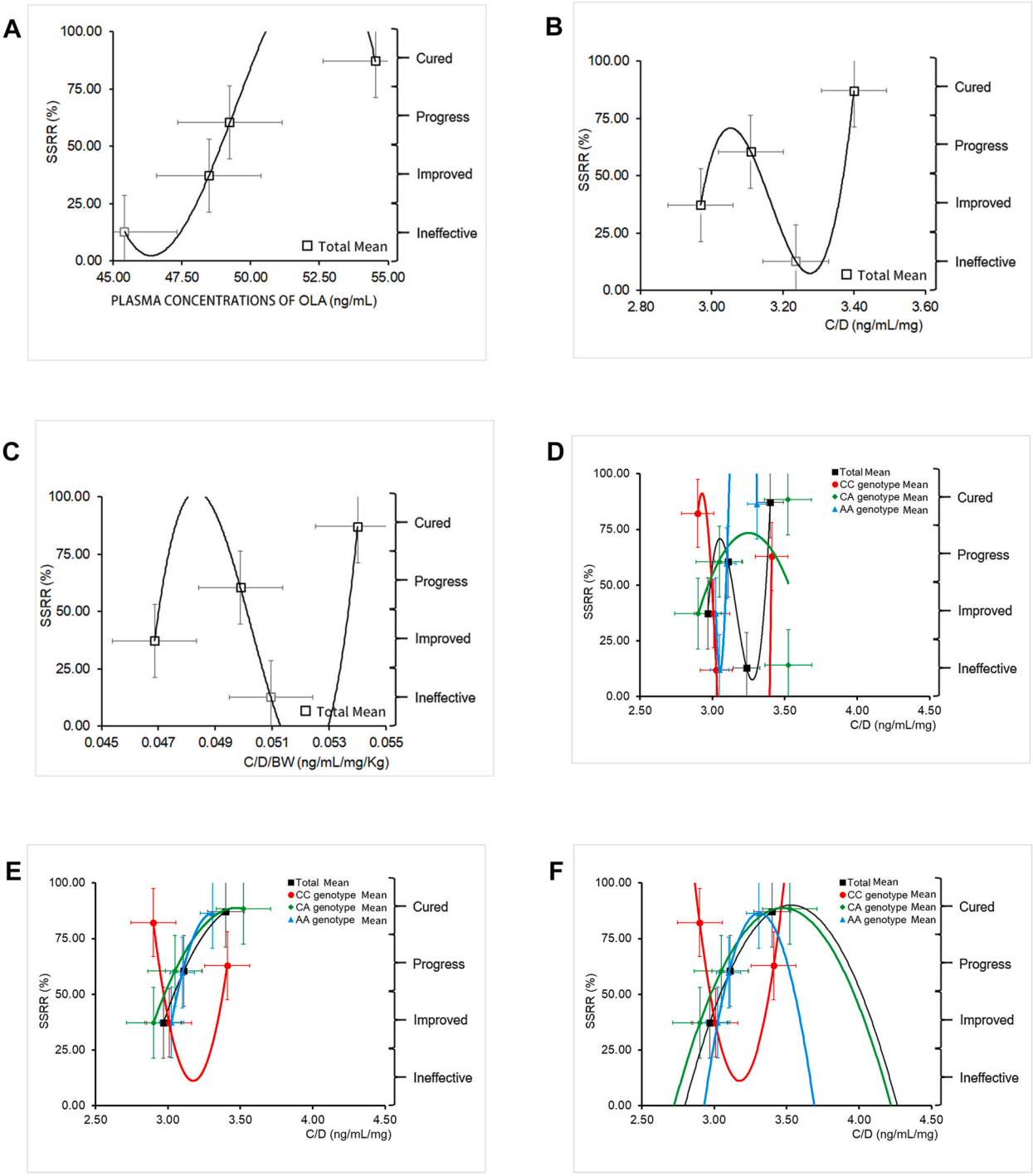

Fig. 3. The relationship between OLA, C/D, C/D/BW and SSRR under total subjects, and the relationship between C/D and SSRR under different CYP1A2 -163C/A genotypes. A. The relationship between OLA and SSRR under total subjects, B. The relationship between C/D and SSRR under total subjects, C. The relationship between C/D/BW and SSRR under total subjects, D. The relationship between C/D and SSRR under three CYP1A2 -163C/A genotypes. E. The relationship between C/D and SSRR under three CYP1A2 -163C/A genotypes exclusion ineffective group, F. The relationship between C/D and SSRR under three CYP1A2 -163C/A genotypes exclusion ineffective group, backward and forward one cycle.

total efficacy, under the combined effect of the three genotypes mentioned above, shows that the concentration of olanzapine in the ineffective group is included in the concentration range of other efficacy responsive groups. It is precisely because of the lack of regularity in the ineffective group in Fig. 3D that consider removing the ineffective group and analyzing the trend again.

When remove ineffective subjects (ineffective group), The results of the total subjects, CA genotype and AA genotype and total showed same tendencies with SSRR($r = 1.000$, Fig. 3E), The higher the C/D value, the better the therapeutic effect. The effective C/D value starts from 2.5 and ends at 4.0, depending on the dosage of 5–20 mg, corresponding to a concentration range of 12.5–80 ng/mL. But the CC genotype different, shows that within the above range, the smaller the C/D value, may be both exists results corresponding to the worse or/and better the therapeutic effect.

Fig. 3E were extended according to the fitting curve for one cycle forward and backwardto draw Fig. 3F. Fig. 3F all genotypes except CC genotype showed downward open parabolic line. The result of CC genotype showed upward open parabolic line with SSRR ($r = 1.000$, Fig. 3F).

The result of Fig. 3F consistent with Fig. 3B, equation of C/D to SSRR (Table 4) in total subjects, CA and AA genotypes showed C/D had two values when SSRR was 0. It was just corresponds to the concentration range of OLA in different CA and AA genotype. But equation in CC genotypes showed C/D had two values when SSRR was 100. Therefore, the best C/D range was the area where SSRR increases with the increase of C/D value in genotypes not distinguished, was 3.18–3.53 ng/mL/mg. The best concentration range of OLA was 17.42–57.33 ng/mL. The largest C/D range and concentration range of OLA is CA genotype.

4. Discussion

First, the effect of CYP1A2 -163C/A genotype polymorphism on OLA metabolism. Regarding OLA dose-corrected serum concentrations, a number of studies failed to detect a significant association for the CYP1A2*1F polymorphism [14,15,19,20], we get same results excluded the reason that the small sample size of above reference studies (around 50 patients). The data of this study showed that there was no significant difference in OLA concentration among three genotypes. The values of C/D and C/D/BW of CA genotype which is single point mutation CYP1A2 -163C/A are the largest. The CYP1A2 -163C/A AA genotype defined as "ultrafast metabolism type"(UM). After the OLA concentration is adjusted by dose and body weight, the C/D and C/D/BW values of AA genotype are the lowest indeed. However, there is no statistical difference with other two genotypes, so in clinical interpretation of UM genotype of CYP1A2 on OLA, we should consider that C/D and C/D/BW should be used to explain, but not OLA concentration.

Secondly, the effect of CYP1A2 -163C/A genotype polymorphism on the efficacy of OLA. The effect of OLA on SSRR of three genotypes was consistent tendency with C/D and C/D/BW, but statistically different in three genotypes. The value of SSRR of CA genotype are the largest. So inferred that there is a certain correlation between C/D and SSRR under three genotypes of CYP1A2 -163C/A. According to the four grades of SSRR, the average value of C/D in each grade is counted. However, we didn't get the ideal correlation at first. Later, found that the distribution of values of three genotypes SSRR ineffective group were messy. Considering that this may be that the efficacy of OLA is except affected by affected CYP1A2 -163C/A genotype, but by other efficacy genotypes more, which needs further research in the later stage. After removing the ineffective group, the other three grades showed good correlation. The higher the C/D value, the higher SSRR.

Thirdly, the relationship between OLA concentration and efficacy under different CYP1A2 -163C/A genotypes. Deduced that $y = ax^2 + bx + c$, Y: SSRR, X: C/D equations are perfect applicable to three genotypes, so the optimal C/D value is found. Like from AGNP2017, which only provides 3.20 (conversion factor) applicable to European population, this study gives C/D value as conversion factor applicable to different genotypes of Chinese people, ranging from 3.18 to 3.53. The trend line corresponding to the equation shows that after the value is greater than the optimal C/D value, increasing the administration does not increase the curative effect. The studies by Ghotbi [19] and Kootstra-Ros [20] et al., showed a nonsignificant effect toward lower C/D for the CYP1A2*1F AA genotype. Our study showed not only for CYP1A2*1F AA genotype, but also other two genotype no SSRR difference in lower C/D.

Finally, many scholars have always mentioned that OLA is a "threshold" drug. Its drug concentration crosses the "threshold" and there is no need to increase the dose. The fact is that there has been no clear evidence. our results clearly indicate that, SSRR under CYP1A2 -163C/A genotype as the evaluation index for the first time, obtains the inflection point of C/D value, so then calculates the inflection point of OLA concentration, This is the first time to clarify the "threshold" of OLA.

The naturalistic and retrospective study design is a limitation of this research, although this design allows a realistic reflection of natural practice. But, we cannot completely exclude that concurrent use of other drugs [21] and dietary chemicals has biased our result.

There is no doubt that study illuminate the influence of CYP1A2*1F polymorphism (−163C.A, rs762551) for individualized medication of olanzapine. Basic proved olanzapine is a "threshold" drug.

As the starting point of China's inland Silk Road, Xi'an is also the place where people have exchanged logistics and human flows for nearly two thousand years. Therefore, the characteristics of the population here may only represent this place, but may also represent China, East Asia, and even Eurasia. Therefore, external validity in other regions and ethnicities is not mentioned in this study conclusions and requires further study. The conclusions may only apply to certain racial groups within Northwest China.

CRediT authorship contribution statement

Yan Zhang: Writing – review & editing, Writing – original draft, Project administration, Formal analysis, Data curation, Conceptualization. **Lisha Sun:** Resources, Investigation, Data curation. **Yanli Su:** Writing – review & editing, Writing – original draft, Conceptualization. **Hui Wang:** Writing – review & editing, Investigation, Data curation.

Table 4
Equation of C/D to SSRR in 3 genotype of CYP1A2 (CYP1A2*1F).

Genotype (CYP1A2*1F)	Equation ($y = ax^2+bx + c$, y:SSRR, x:C/D)	r	C/D(ng/mL/mg)				OLA (ng/mL)
			y = 0		y = max	Optimal	
total	$y = -167.55x^2+1182.9x-1997.8$	1.000	2.797	4.263	3.530	3.18–3.53	13.99–85.26
CC	$y = 936.48x^2-5946.4x+9450.5$	1.000	y = 100		y = min		**17.42–57.33**
			3.483	2.867	3.175		
CA	$y = -158.12x^2 + 1097.9x - 1817$	1.000	2.722	4.221	3.472		**13.61**–84.42
AA	$y = -600.08x^2+3973.6x-6491.7$	1.000	2.931	3.690	3.311		14.66–73.81

Data availability statement

The data that supports the findings of this study are available in the supplementary material of this article.

Declaration of competing interest

Enclosed herewith is the manuscript entitled "**A 6-year retrospective study of olanzapine plasma concentration inpatients with schizophrenia CYP1A2 polymorphisms in real-life settings** ". Yan Zhang, Lisha Sun, Yanli Su, Hui Wang are entire authors. We promise that the submitted manuscript hasn't been previously published, or is under consideration elsewhere. The entire authors declare no competing financial and achievements interests.

This study was reviewed and approved by the ethics committee of Xi'an mental health center (xajwky-201801), and followed the principles of the Helsinki declaration.

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