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Research article

Effects of *CYP2D6* gene polymorphism on plasma concentration and therapeutic effect of olanzapine

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ABSTRACT

This study aimed to evaluate the relationship between gene polymorphisms of metabolic enzymes, particularly the *CYP2D6* gene, and the plasma concentration of olanzapine, as well as treatment response in patients with chronic schizophrenia. We recruited olanzapine-treated patients and examined their plasma olanzapine levels. Additionally, a common mutation site within each of the nine exons of the full-length *CYP2D6* sequence was assayed. The Positive and Negative Syndrome Scale, Brief Psychiatric Rating Scale, and Overall Clinical Impression were used to assess schizophrenic symptoms, whereas the Barnes Akathisia Scale and Extrapyramidal Symptom Rating Scale were used to evaluate adverse effects. The results showed no significant differences in plasma olanzapine concentrations, treatment response, or the occurrence of adverse effects among different *CYP2D6* genotypes. However, an association between olanzapine concentrations and improvement in clinical symptoms and adverse reactions was observed. In conclusion, the CYP2D6 genotype did not significantly impact plasma olanzapine concentrations, treatment response, or the occurrence of adverse effects.

1. Introduction

Olanzapine, an atypical antipsychotic, is widely used to treat psychiatric disorders due to its effectiveness in addressing both positive and negative symptoms of schizophrenia, outperforming first-generation antipsychotics [1,2]. Moreover, olanzapine is associated with a decreased risk of extrapyramidal side effects and tardive dyskinesia but is associated with a high prevalence of metabolic disorders, such as weight gain, dyslipidemia, and insulin resistance [3]. Despite its widespread clinical use, a high percentage of patients with schizophrenia respond poorly to olanzapine treatment or present with refractory schizophrenia. In addition, side effects that develop during treatment can significantly influence the treatment outcome and often limit the use of olanzapine.

Inter-individual differences in clinical response to olanzapine treatment are one of the most challenging issues in clinical psychiatry. This variability can be attributed to the substantial inter-individual variability in olanzapine pharmacokinetics, resulting in a wide range of plasma drug concentrations after administration (4–10-fold) [4,5]. The plasma concentrations of olanzapine have been associated with improvements in clinical symptoms of patients with schizophrenia [6,7], as well as the occurrence of adverse effects such as weight gain [8], hyperinsulinemia, hyperlipidemia [9] and abnormal prolactin levels [10]. In a double-blind olanzapine trial, it

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was found that an olanzapine concentration ≥23.2 ng/mL can predict the therapeutic response [11]. Several factors, including sex, smoking, and age, can influence the plasma concentrations of olanzapine [12,13]. In addition, genetic polymorphism of the drug-metabolizing enzymes may also contribute to inter-individual variations in plasma levels of antipsychotics.

Olanzapine undergoes extensive and complex metabolism through a number of enzymatic pathways. The polymorphic CYP2D6 is involved in the metabolism of olanzapine to 2-hydroxymethylolanzapine, a minor metabolite [14]. Nonetheless, the role of CYP2D6 in the clinical pharmacokinetics of olanzapine remains unclear. Although a previous review suggested that poor metabolizers (PMs) would have decreased clearance of olanzapine compared with extensive metabolizers (EMs) [15], others have found no association between *CYP2D6* genotype and the pharmacokinetics of olanzapine [16]. A previous study reported that patients receiving olanzapine along with CYP2D6 enzyme inhibitors had approximately 40% higher concentrations compared to those receiving olanzapine alone [17]. Therefore, the precise relationship between *CYP2D6* genotype and olanzapine pharmacokinetics requires further investigation. Additionally, most studies on CYP2D6 enzyme pharmacogenetics have focused on olanzapine disposition, whereas the connection between pharmacogenetics and clinical treatment response or adverse effects resulting from olanzapine treatment remains uninvestigated. Only one clinical study explored the correlation between clinical improvement, olanzapine plasma concentration, and pharmacogenetics and found no association between improved total Brief Psychiatric Rating Scale (BPRS) scores and olanzapine plasma concentration. However, significant associations between individual BPRS scores for symptoms like suspiciousness, hallucinations, and blunted affect and olanzapine plasma concentration were observed [16]. Therefore, further investigation is needed to determine whether a definitive relationship exists between olanzapine plasma concentration and clinical symptoms or adverse reactions based on pharmacogenetics.

In this study, we focused on a common mutation site within each of the nine exons of the full-length *CYP2D6* gene, which allowed for a more comprehensive analysis of *CYP2D6* genotypes. The primary aim of this study was to evaluate the role of *CYP2D6* variants on plasma olanzapine concentrations and treatment response in patients with schizophrenia. The secondary objective was to investigate the relationship between plasma olanzapine concentration and the clinical symptoms as well as adverse reactions experienced by patients with schizophrenia.

2. Materials and methods

2.1. Patients and methods

This study was approved by the Ethics Committee of the Third People's Hospital of Jiangyin City. The paper version of the ethics review report was signed on August 28, 2017. A total of 76 patients with chronic schizophrenia, aged 18–68 years and diagnosed according to the International Classification of Diseases, tenth edition (ICD-10), were enrolled in the study. All participants were fully informed about the study's purpose and provided written consent following the principles of the Declaration of Helsinki.

The participants were recruited from inpatients at the Third People's Hospital of Jiangyin City, Jiangsu Province, between May 2018 and May 2019. The average duration of the disease was 13.48 ± 7.80 years. The study included patients who met the diagnostic criteria for schizophrenia according to the ICD-10, patients with schizophrenia who have had an illness duration exceeding 5 years, were in remission prior to hospitalization, have not used any antipsychotic medications in the last year, and were hospitalized again due to an acute attack and subsequently treated with olanzapine monotherapy. Olanzapine was initially administered at a low dosage and then progressively increased to a therapeutic level of 5–27.5 mg/d.

Exclusion criteria included electroconvulsive therapy within 3 months before admission, use of other psychiatric drugs (including antidepressants and mood stabilizers), apparent brain damage or serious physical illness, and other conditions such as the use of antiallergic drugs or participation in other clinical trials within 3 months before enrollment. Initially, 80 patients were included in the study, but two dropped out due to drug adjustments and two due to poor compliance. Consequently, the final analysis included 76 patients.

General information was collected from all participants at the study's baseline, including relevant demographics, weight, height, clinical assessment of mental symptoms, laboratory tests, comprehensive medical history, and detection of *CYP2D6* genotypes. Psychiatric symptoms were evaluated using the Positive and Negative Syndrome Scale (PANSS), BPRS, and Clinical Global Impression (CGI). Experienced psychiatrists, who underwent scale consistency training, conducted the clinical assessments. The inter-evaluator consistency was over 80% after training. Adverse effects were assessed using the Barnes Akathisia Scale (BAS) and the Extrapyramidal Symptom Rating Scale (ESRS). Laboratory parameters included fasting low-density lipoprotein-C, cholesterol, high-density lipoprotein (HDL)-C, triglyceride, glucose, liver and renal function tests, prolactin, and electrocardiogram. Follow-up evaluations were conducted at 2, 4, and 8 weeks after treatment. During each follow-up visit, baseline evaluation indicators, with the exception of demographics and *CYP2D6* genotypes, were repeated. Additionally, olanzapine concentrations were measured at each follow-up. Data collectors had access to identifiable participant information during and after data collection. The primary variables were olanzapine concentrations in different *CYP2D6* genotypes and *CYP2D6* gene single-nucleotide polymorphisms (SNPs), as well as clinical symptoms at 2, 4, and 8 weeks. The secondary indicator was adverse reactions at 4 and 8 weeks.

2.2. Determination of the plasma concentrations of olanzapine

All blood samples were collected from patients between 7 a.m. and 9 a.m. after an overnight fast. The blood sampling for olanzapine was consistently performed before the next administration of the drug, and the timing of blood collection was consistent at 2, 4, and 8 weeks. Plasma samples were stored at −20 °C until analysis. The steady-state plasma concentrations of olanzapine were

measured using high-performance liquid chromatography with an Agilent 1260 HPLC system (Agilent, 1260 HPLC, USA) as previously described [18]. Briefly, olanzapine was extracted from 200 μL plasma samples using *tert*-butyl methylether; olanzapine-D3 served as the internal standard. Quantification of the analytes was achieved via linear gradient-reversed phase chromatography, coupled with tandem mass spectrometry detection operating in positive electrospray ionization mode, utilizing multiple reaction monitoring. Linear calibration curves for olanzapine were obtained within the concentration ranges of 5–100 ng/mL. The detection limits of olanzapine were 0.4 ng/mL. The intra- and inter-day precision and relative errors were <15%. The olanzapine concentration–dose (C/D) ratio is a potential predictor of the effectiveness of the drug in patients with schizophrenia [19]. Therefore, we further investigated the relationship between the olanzapine C/D ratio and the polymorphisms of metabolizing enzymes. The C/D ratio (ng/ml per mg/day) was calculated by dividing the total concentration of olanzapine, in ng/mL, by the olanzapine dose, in mg/day.

2.3. CYP2D6 genotyping and predicted phenotypes

Blood samples were stored at −70 °C for subsequent genomic DNA extraction and pharmacogenetic analyses. Genomic DNA was extracted using the YC-B nucleic acid extraction reagent (Hygeianecy Biological, Wuhan, China). DNA concentration and purity were evaluated using absorbance methodology with a NanoDrop 1000 Spectrophotometer V3.7 (Thermo Fisher Scientific, Waltham, MA, USA). The polymerase chain reaction (PCR) assays, followed by targeted sequencing, were conducted to determine *CYP2D6* genotypes in all patients. The current study encompassed the detection of all nine exons of the *CYP2D6* gene. The complete experimental procedure encompassed primer design, PCR, and sequencing. Oligo6 software was utilized to design four sets of upstream and downstream primers to amplify the nine exons, employing genomic DNA as the template. The details of individual PCR programs are summarized in Supplementary Table 1. Sequencing was performed using a 3730xl DNA Analyzer (Applied Biosystems, USA), and the results were analyzed using GeneMapper software. Star (*) allele designations were assigned according to the Human Cytochrome P450 (CYP) Allele Nomenclature Database (http://www.cypalleles.ki.se/). The *CYP2D6*1* allele was set when no nucleotide change was observed in all genotyped SNPs. Patients with two low-activity alleles were classified as intermediate metabolizers (IMs), whereas those with one low-activity allele and one or two functional alleles were classified as EMs as previously reported [20].

2.4. Statistical analysis

Statistical analysis was conducted using SPSS 23.0 software (SPSS version 23, Chicago). Two-tailed p-values below 0.05 were considered statistically significant. Normally distributed continuous variables were expressed as mean ± standard deviation, whereas non-normal distributions were presented as median ± interquartile ranges. The *t*-test or analysis of variance was used to compare normally distributed data, and the Mann–Whitney *U* test was used for non-normally distributed data. For multiple group comparisons, the Kruskal–Wallis test was utilized. The chi-square test was performed to compare categorical variables. The Dunn–Bonferroni post-hoc test was employed to compare inter-group differences. The correlations between clinical treatment response (The changes in PANSS total score and subscale scores), changes in adverse reactions and plasma olanzapine concentrations were determined using Pearson or Spearman correlation analysis. Multiple comparisons were corrected using Bonferroni correction. All genotypes were checked for deviation from Hardy–Weinberg equilibrium.

3. Results

3.1. Demographic and genotypic characteristics

The *CYP2D6* SNPs 100C > T, 1038C > T, 1662 G > C, 2851C > T, and 4181 G > C were detected in this study, as shown in Table 1. The demographic and clinical details of the study participants according to *CYP2D6* phenotype are shown in Supplementary Table 1. SNP/allele frequencies detected were as follows: 100C > T = 72.3%, 1038C > T = 75%, 1662 G > C = 80.2%, 2851C > T = 32.9%, and

Table 1
Frequency distribution of *CYP2D6* SNPs, alleles, and phenotypes.

Variant	ID SNP	Frequency (%)	CYP2D6 allele	Allele function	Allele frequency (%)	Diplotype	Predicted phenotype	frequency (%)
100C > T	rs1065852	55 (72.3%)	1*	Functional	9 (11.8)	*1/*1	EM	9 (11.8)
1038C > T	rs1081003	57 (75%)	2*	Functional	9(11.8)	*1/*34	EM	1(1.3)
1662 G > C	rs1058164	61 (80.2%)	10*	Reduced function	39(51.3)	*1/*39	EM	2(2.6)
2851C > T	rs16947	25 (32.9%)	34*	Functional	1(1.3)	*2/*2	EM	2(2.6)
G4181 G > C	rs1135840	61 (86.9%)	39*	Functional	3(3.9)	*2/*34	EM	5(6.5)
			65*	Unknown	15(19.7)	*2/*39	EM	2(2.6)
						*10/*10	IM	25(32.9)
						*10/*39	EM	14(18.4)
						*39/*39	EM	1(1.3)
						*10/*65	Unknown	15(19.7)

Abbreviations: SNPs, single nucleotide polymorphisms; EM, extensive metabolizer; IM, intermediate metabolizer.

4181 G > C = 86.9%. *CYP2D6* alleles were designated according to the *CYP2D6* Allele Nomenclature Database; relevant information for the identified *CYP2D6* alleles is described in Supplemental Table 2. For instance, the presence of two SNPs 100C > T and 4180 G > C was confirmatory of genotype *CYP2D6*10*. *CYP2D6* allele functions were assessed using the "*CYP2D6* Allele Functionality Table" through the PharmGKB (https://www.pharmgkb.org/page/cyp2d6RefMaterials). In total, 6 *CYP2D6* alleles were identified in 76 patients, consisting of four functional alleles (*CYP2D6*1*, *CYP2D6*2*, *CYP2D6*34*, and *CYP2D6*39*), one reduced-function allele (*CYP2D6*10*), and a new unknown-function allele (*CYP2D6*65*) as shown in Table 1. No allele frequencies deviated from Hardy–Weinberg equilibrium. In addition, phenotypes were classified as follows: *CYP2D6*1/*1* (n = 9; 11.8%), *CYP2D6*1/*34* (n = 1; 1.3%),*CYP2D6*1/*39*(n = 2; 2.6%),*CYP2D6*2/*2* (n = 2; 2.6%), *CYP2D6*2/*34* (n = 5; 6.5%), *CYP2D6*2/*39* (n = 2; 2.6%), *CYP2D6*10/*39* (n = 14; 118.4%), and *CYP2D6*39/*39* (n = 1; 1.3%) were classified as EMs; *CYP2D6*10/*10* (n = 25; 32.9%) were classified as IMs; and *CYP2D6*10/*65* (n = 15; 19.7%) were classified as Unknowns. Finally, 47.4% (36/76) were classified as EMs, 32.9% (25/76) as IMs, and 19.7% (15/76) as Unknown. The *CYP2D6* genotypes and predicted phenotypes in the 67 patients are presented in Table 1.

3.2. Demographic and olanzapine plasma concentrations between different CYP2D6 phenotypes

The demographic and clinical details of different *CYP2D6* phenotypes are shown in Supplemental Table 3. No significant difference was observed in terms of age, weight, olanzapine dose, or scores of various clinical symptom assessment scales at baseline. Interestingly, a significant difference in sex was found among the three groups, with a significantly higher proportion of female patients in the Unknown group compared to the other two groups; this was included as a covariate in subsequent analyses. The EMs group showed a trend of lower olanzapine plasma concentrations and C/D ratios than the IMs group at different time points (Fig. 1A and B). Interestingly, the olanzapine concentration in the Unknowns group exhibited a noticeable decrease at 8 weeks, leading to a lower trend of concentrations compared to the other two groups (Fig. 1A and B). However, the difference was not statistically significant.

3.3. Differences in clinical symptom improvement and adverse reactions among different CYP2D6 phenotypes

The improvement in clinical symptoms was measured by the changes in PANSS scores relative to baseline at 2, 4, and 8 weeks. The differences in symptom improvement among *CYP2D6* phenotypes are presented in (Table 2). No significant differences were observed in improvement in PANSS total score, PANSS-positive subscale total score, PANSS-negative subscale total score, and PANSS-general subscale total score among different genotypes at 2, 4, and 8 weeks. However, the improvement in the PANSS-general subscale total score showed a lower trend compared to the other two groups at week 8. We also investigated differences in adverse effects among predicted *CYP2D6* phenotypes (Table 3). Changes in TG levels from baseline to weeks 4 and 8 were higher in the EMs and Unknowns groups than in the IMs group ($F = 7.099$, $p = 0.002$, $F = 3.540$, $p = 0.035$). No difference was found in the other adverse reactions among different groups.

3.4. Correlation between olanzapine concentration and clinical symptoms and adverse effects

We also investigated the relationship between olanzapine concentrations and improvement in clinical symptoms (Fig. 2). Our analysis revealed a significant correlation between olanzapine concentration and improvement in PANSS total score at week 8 ($r = 0.269$, $p = 0.033$) (Fig. 2I), but not at weeks 2 and 4 (both $p > 0.05$) (Fig. 2A and E). However, the difference did not pass Bonferroni's correction. Further clinical subscale correlation analysis revealed a significant correlation between improvement in PANSS-general subscale total score and olanzapine concentration at week 8 ($r = 0.406$, $p = 0.001$) (Fig. 2L), and the significance was adjusted via Bonferroni correction. The relationship between drug concentration and adverse effects was also explored (Supplementary Table 4).

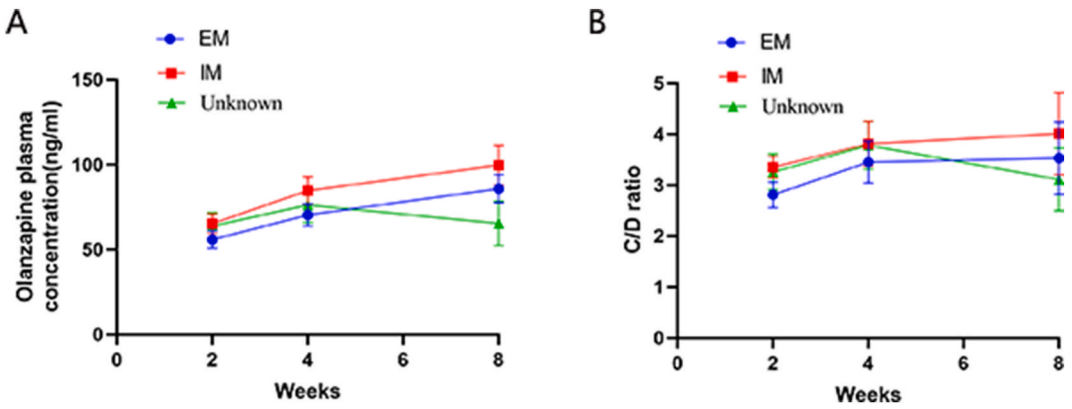

Fig. 1. Drug concentrations and C/D ratios among different *CYP2D6* phenotypes. Abbreviations: EMs, Extensive metabolizers; IMs, Intermediate metabolizers. C/D, concentration/dose.

Table 2
Psychopathological symptoms measure according to the predicted *CYP2D6* phenotype.

Symptom measure	EMs(N = 36)	IMs (N = 25)	*Unknowns(N = 15)*	Statistics	Adjusted P value[a]
PANSS total score					
Week 0-Week 2	11.33 ± 8.49	11.80 ± 11.03	10.87 ± 9.13	0.047	0.955
Week 0-Week 4	20.20 ± 9.09	19.45 ± 14.12	19.21 ± 13.18	0.048	0.953
Week 0-week 8	29.93 ± 11.69	28.65 ± 17.60	27.78 ± 15.99	0.113	0.893
PANSS-positive subscale total score					
Week0-week 2	5.81 ± 3.42	4.64 ± 5.23	5.27 ± 3.15	0.609	0.547
Week0-week 4	10.74 ± 4.49	10.86 ± 6.37	9.21 ± 5.69	0.487	0.616
Week0-week 8	13.60 ± 4.70	14.00 ± 6.15	12.64 ± 5.12	0.279	0.757
PANSS-negative subscale total score					
Week0-week 2	3.00 ± 4.79	4.24 ± 5.29	3.30 ± 4.82	0.765	0.469
Week0-week 4	7.29 ± 6.03	6.77 ± 8.85	5.71 ± 6.32	0.248	0.781
Week0-week 8	5.93 ± 7.03	6.65 ± 7.86	10.36 ± 7.12	0.523	0.595
PANSS-general subscale total score					
Week 0-week 2	2.53 ± 6.59	2.92 ± 5.60	3.13 ± 7.51	0.055	0.946
Week 0-week 4	2.17 ± 7.52	1.82 ± 9.11	3.85 ± 7.19	0.284	0.753
Week 0-week 8	11.45 ± 8.41	8.00 ± 8.19	4.78 ± 9.93	0.870	0.424

Abbreviations: EMs, Extensive metabolizers; IMs, Intermediate metabolizers; PANSS, Positive and Negative Syndrome Scale.
[a] Adjusted P value after sex correction.

Table 3
Adverse effects measure according to the predicted CYP2D6 phenotype.

Adverse effects	EMs(N = 36)	IMs(N = 25)	*Unknowns(N = 15)*	Statistics	Adjusted P value[a]
Weight change from week 0–4, kg	−0.41 ± 1.50	−0.59 ± 2.14	0.29 ± 1.14	1.263	0.289
Weight change from week 0–8	−0.63 ± 8.49	−4.50 ± 4.65	1.57 ± 3.36	2.231	0.116
GLU change from week 0–4, mmol/L	−0.24 ± 1.01	−0.65 ± 1.87	0.07 ± 1.21	1.239	0.296
GLU change from week 0–8	−0.14 ± 0.17	−0.11 ± 1.47	−0.06 ± 1.45	0.016	0.984
TG change from week 0–4, mmol/L	0.95 ± 1.30	0.01 ± 0.95	1.40 ± 1.12	7.099	0.002
TG change from week 0–8	0.26 ± 1.74	−0.14 ± 2.00	1.20 ± 1.28	3.540	0.035
CHO change from week 0–4, mmol/L	0.28 ± 1.28	−0.17 ± 1.17	0.65 ± 1.67	1.721	0.187
CHO change from week 0–8	0.14 ± 1.11	0.04 ± 0.99	0.63 ± 1.74	1.014	0.369
LDL change from week 0–4, mmol/L	0.26 ± 0.82	0.25 ± 0.75	0.44 ± 0.78	0.291	0.749
LDL change from week 0–8	0.20 ± 0.83	0.72 ± 0.87	0.44 ± 0.76	2.303	0.109
HDL change from week 0–4, mmol/L	−0.09 ± 0.26	−0.15 ± 0.31	−0.26 ± 0.22	0.911	0.407
HDL change from week 0–8	−0.05 ± 0.33	−0.07 ± 0.31	0.01 ± 0.46	0.219	0.804
PRL change from week 0–4, mmol/L	13.63 ± 33.29	23.95 ± 47.63	41.60 ± 60.64	1.921	0.155
PRL change from week 0–8	10.62 ± 34.60	25.15 ± 34.71	28.07 ± 56.18	1.191	0.311
ESRS Week 4	8(22.2%)	6(24.0%)	3(20%)	0.143	0.843
ESRS Week 8	7(19.4%)	4(16%)	3(20%)	0.038	0.963
BAS Week 4	2(5.5%)	1(4.0%)	1(6.7%)	0.870	0.424
BAS Week 8	3(8.3%)	1(4.0%)	1(6.7%)	2.037	0.729

Abbreviations: EMs, Extensive metabolizers; IMs, Intermediate metabolizers; GLU, glucose; TG, triglyceride; CHO, cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; PRL, prolactin; ESRS, Extrapyramidal Symptom Rating Scale; BAS, Barnes Akathisia Scale.
[a] Adjusted P value after sex correction.

Significant correlations were identified between olanzapine concentration and changes in glucose at week 4 after Bonferroni correction ($r = 0.320$, $p = 0.008$). Additionally, we observed a clear negative correlation between olanzapine concentration and changes in HDL at week 8 ($r = -0.279$, $p = 0.028$), but a positive correlation between olanzapine concentration and changes in prolactin at week 8 ($r = 0.312$, $p = 0.015$); however, these correlations did not pass the correction test.

4. Discussion

The results of the present study indicated that the *CYP2D6* genotype did not significantly impact olanzapine plasma concentrations, treatment response, or occurrence of adverse effects. However, olanzapine concentrations were associated with psychopathological symptoms and adverse effects in olanzapine-treated patients.

In our cohort of patients, *CYP2D6*10* was the most common allele at 51.3%. This is consistent with the previously reported frequency of 43.6% in East Asian populations [21]. As we did not perform *CYP2D6* gene deletion and duplication, PMs and UMs could not be identified. A previous study conducted on patients with schizophrenia found that in 2.2% of patients with *CYP2D6**5(gene deletion) and *CYP2D6**6, *CYP2D6* duplicated alleles were found at frequencies of 0.7% (*1X2 and *2X2) and 0.3% (*4X2), suggesting the under-representation of PMs and UMs in the cohort of patients with schizophrenia [22]. Considering the low frequency of *CYP2D6* gene deletion and duplications presented in patients with schizophrenia, as well as the small sample size of the cohort analyzed in the current study, the omission of deletion and duplication detection is likely to negligibly impact our results.

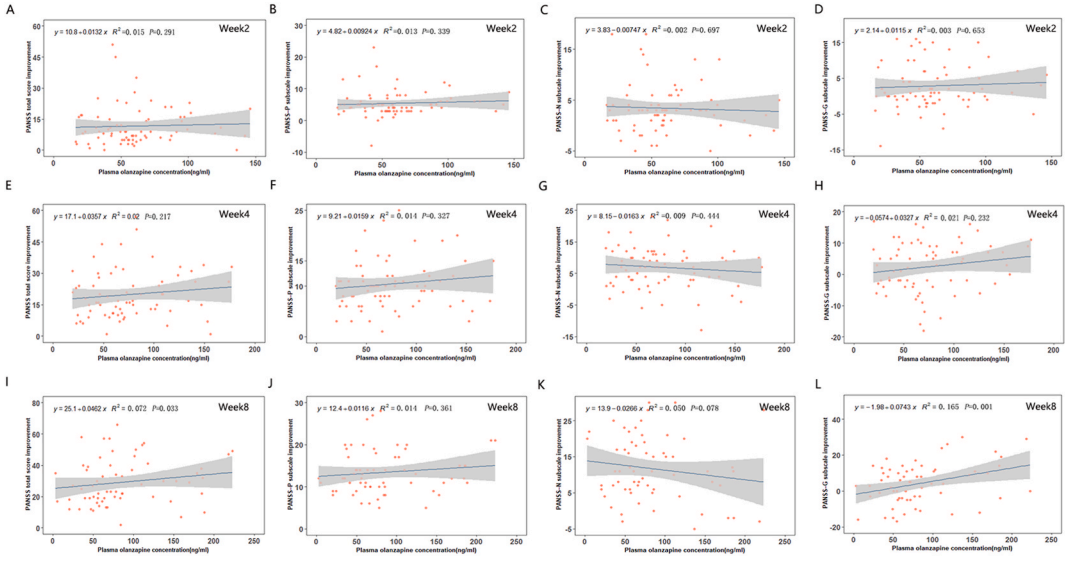

Fig. 2. The correlation between different psychopathological symptoms and plasma olanzapine concentration. A–D: The correlation between plasma olanzapine concentration and PANSS total score improvement (A), PANSS–positive subscale total score improvement (B), PANSS-negative subscale total score improvement (C), PANSS-general subscale total score(D) at week2, respectively; E–H: The correlation between plasma olanzapine concentration and PANSS total score improvement (E), PANSS–positive subscale total score improvement (F), PANSS-negative subscale total score improvement (G), PANSS-general subscale total score improvement (H) at week4, respectively; I–L: The correlation between plasma olanzapine concentration and PANSS total score improvement (I), PANSS–positive subscale total score improvement (G), PANSS-negative subscale total score improvement (K), PANSS-general subscale total score improvement (L) at week8, respectively. According to the Bonferroni correction, the PANSS-general subscale total score improvement passed the correction. Abbreviations: PANSS: Positive and Negative Syndrome Scale.

Current study found no association between *CYP2D6* genotype and the pharmacokinetics of olanzapine. By analyzing our cohort, we found lower clearance of olanzapine in IM patients than in EM patients; however, the difference was not statistically significant, which is consistent with previous research reported that olanzapine clearance is not affected by the *CYP2D6* genotype [16,23]. However, our results contradict a few earlier studies that reported a correlation between *CYP2D6* genotypes and olanzapine plasmatic concentrations, which found a significant influence of the *CYP2D6* genotype on the prescribed daily olanzapine dose when smoking habits were considered, with EMs having higher doses than PMs [18]. The current study reported a novel *CYP2D6*65* allele whose phenotypic translation is currently undetermined. Intriguingly, olanzapine plasmatic concentrations in the patients with unknown-phenotype were lower than those in IM and EM patients. Although this difference was not statistically significant, it suggested a higher clearance of olanzapine in patients harboring the *CYP2D6*65* allele.

Our study revealed that the *CYP2D6* genotype may not be an effective predictor of improvement in clinical symptoms and susceptibility to antipsychotic-induced adverse effects. The improvement in both the PANSS total score and subscales did not show significant differences between phenotypes. This is consistent with previous studies on the association between *CYP2D6* polymorphism and olanzapine treatment response [24]. However, a recent study found that olanzapine treatment outcomes are influenced by factors such as dose, sex, age, and CYP2D6 metabolizer status [25]. Notably, a trend of lower improvement in the general subscale of the PANSS scale was observed in the Unknowns group compared with the PMs and IMs groups. However, the difference was not statistically significant, which may be attributed to the small sample size of our cohort. Nonetheless, these results suggest that different *CYP2D6* metabolic phenotypes may impact a specific dimension of psychiatric symptoms in patients with schizophrenia. In our study, patients in the Unknowns group had a significantly higher increase in TG than those in the EMs and IMs groups, suggesting that different CYP2D6 metabolic phenotypes may affect lipid metabolism abnormalities induced by olanzapine treatment. However, no differences in weight changes were observed between different metabolic phenotypes, which is inconsistent with a previous study that suggested *CYP2D6* polymorphism as a reliable predictor of the correlation between olanzapine and weight gain in patients with psychosis [26]. These discrepancies may be attributed to the small sample size of our cohort. Nevertheless, another study that included a more comprehensive range of *CYP2D6* genotypes (*CYP2D6*3*, **4*, **6*, **7*, **8*, **9*, **10*, **14*, **17*, **41*) supported our findings, suggesting that CYP2D6 phenotype is not related to adverse reactions induced by olanzapine [27].

A significant association was observed between olanzapine plasma concentration and improvement in PANSS total score at week 8, as well as PANSS-general subscale total score. This finding aligns with previous studies that have identified olanzapine concentration as a predictor of clinical symptoms [6,28]. A recent study showed that olanzapine blood concentration at different times of treatment was positively related to the treatment effect of patients with schizophrenia [29]. However, this result contradicts the findings of a recent study that showed no correlation between olanzapine concentrations and improvement in psychotic symptoms [30]. The possible explanation for this contradiction is the differences between age, group, severity, and daily-defined dose between the two studies. In addition, we found that improvements in PANSS-general subscale total score were positively correlated with plasma

olanzapine concentrations at week 8, which may be attributed to specific components of the clinical response related to the binding to different receptors. However, we did not determine the receptor binding rate for different receptors; therefore, accurately inferring the relationship between the binding of olanzapine to different receptors and the improvement of clinical symptoms is unfeasible. Our results showed that the use of an adequate olanzapine dose may be required to improve symptoms within the therapeutic dose range, suggesting that therapeutic drug monitoring of olanzapine could help evaluate therapeutic efficacy [27]. Similarly, our correlation analysis indicated a significant relationship between olanzapine plasmatic concentrations and adverse effects. This finding is consistent with a previous report that described higher olanzapine concentrations in patients experiencing adverse effects [31]. In our study, we also observed a positive association between concentration and changes in glucose. However, other studies have reported no association between adverse effects and plasmatic concentrations of olanzapine [28,30]. Possible reasons for these discrepancies may include heterogeneity in the disease course and variations in drug dosage. Therefore, further verification is necessary to establish an accurate association between olanzapine concentration and adverse effects.

The current study has certain limitations that should be acknowledged. The main limitation is the small sample size, which may affect the generalizability of the findings. Another limitation is the relatively short duration of our follow-up, lasting only 8 weeks. This limited timeframe hampers our ability to investigate the long-term effects of olanzapine treatment on clinical symptoms and adverse reactions in relation to pharmacogenetics. Additionally, the accuracy of characterizing different metabolic phenotypes using *CYP2D6* genotypes in our research is challenging, considering that *CYP2D6*65* is relatively frequent and its phenotypic translation is currently undetermined. Furthermore, we did not measure *CYP2D6* gene deletion and *CYP2D6** duplication, which might affect the determination of our genetic phenotype. To address these limitations and provide a more comprehensive understanding, future research should include long-term studies in a larger cohort with more comprehensive sets of genotypes.

5. Conclusions

Overall, the findings from our study indicate a correlation between the plasma concentration of olanzapine and clinical symptoms, as well as certain adverse reactions. However, the *CYP2D6* gene polymorphism may not affect the olanzapine blood concentration and therapeutic effect.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the third people's Hospital of Jiangyin City on August 28, 2017. All participants (or their legal guardians) provided informed consent to participate in the study.

Data availability

The datasets used are available from the corresponding author on reasonable request.

CRediT authorship contribution statement

Ye Yang: Writing – original draft, Data curation, Formal analysis. **Wenqing Liu:** Conceptualization, Methodology. **Renrong Wu:** Writing – review & editing, Supervision, Project administration, 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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e28832.

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