Intelligent Pharmacy 4 (2026) 275–280

Contents lists available at ScienceDirect

Intelligent Pharmacy

journal homepage: www.keaipublishing.com/en/journals/intelligent-pharmacy

Full length article

Analysis of influencing factors on the steady-state concentration/dose ratio of vortioxetine based on therapeutic drug monitoring

Xiaoqian Lan, Hongyan Zhuang, Shuang Bao, Mengxi Niu, Yannan Zang, Fei Jia, Pengfei Li*

Beijing Key Laboratory of Intelligent Drug Research and Development for Mental Disorders, National Clinical Research Center for Mental Disorders, National Center for Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, 100088, China

ARTICLE INFO

Keywords:
Vortioxetine
Therapeutic drug monitoring
Steady-state concentration
Influencing factors

ABSTRACT

Objective: To investigate the influencing factors of the steady-state concentration/dose ratio (C/D) of vortioxetine and promote individualized and rational use of vortioxetine.

Methods: All inpatients who received therapeutic drug monitoring (TDM) of vortioxetine in our hospital from July 2022 to December 2025 were included. Basic information such as gender, age, body mass index (BMI), and *CYP2D6* genotype, as well as drug treatment information including dosage and concomitant medications, was collected through the electronic medical record system. Data were statistically analyzed using SPSS 23.0 software.

Results: A total of 109 patients with measured steady-state blood drug concentrations were included in this study. The steady-state blood concentration of vortioxetine was 22.06 (13.26, 35.34) ng·mL^{-1}, and the median (IQR) C/D value was 1.53 (0.97,2.23) ng·mL^{-1}·mg^{-1}·d. The administered dose explained only 26.3% of the variability in vortioxetine plasma concentrations. Concomitant lamotrigine was associated with a lower C/D ratio in univariate analysis ($p < 0.05$), but this association did not remain significant in multivariate analysis ($p = 0.154$).

Conclusions: There is a significant inter-individual pharmacokinetic difference in vortioxetine concentration. The potential effect of lamotrigine on vortioxetine C/D ratio requires further investigation, as the univariate finding was not confirmed in multivariate analysis. It is recommended that patients undergo routine therapeutic drug monitoring to ensure the safety and efficacy of vortioxetine use.

1. Introduction

Vortioxetine is a multimodal antidepressant that acts as a serotonin (5-HT) reuptake inhibitor, while also functioning as an antagonist at 5-HT_3, 5-HT_7, and 5-HT_{1D} receptors, a partial agonist at the 5-HT1B receptor, and a full agonist at the 5-HT_{1A} receptor.[1] The drug was launched in China in April 2018, and its safety and efficacy in the clinical treatment of major depressive disorder have been well established[1,2]. Additionally, due to its cognition-enhancing effects, vortioxetine is also being explored for use in neurological disorders characterized by cognitive impairment.[3]

Therapeutic drug monitoring (TDM) is widely used in clinical practice to facilitate individualized patient medication. According to the consensus guidelines of the Arbeitsgemeinschaft für Neuropsychopharmakologie und Pharmakopsychiatrie (AGNP), vortioxetine has a TDM recommendation level of 2 (recommended), with a therapeutic reference concentration range of 10–40 ng·mL^{-1}.

This study aims to analyze the factors influencing the steady-state concentration/dose (C/D) ratio of vortioxetine based on TDM data, thereby providing a reference for the individualized dosing of vortioxetine.

2. Material and methods

2.1. Study population

All inpatients who underwent TDM for vortioxetine at our hospital from July 2022 to December 2025 were enrolled as study subjects. This study was approved by the Ethics Committee of Beijing Anding Hospital, Capital Medical University (2025 Research No. 178). The requirement for informed consent was waived.

The following patient information was collected: 1) General data: sex, age, height, weight, body mass index (BMI). Patients were classified into underweight (BMI < 18.5), normal weight (BMI 18.5–23.9),

* Corresponding author. 5 Ankang Hutong, Deshengmenwai Avenue, Xicheng District, Beijing, 100088, China.
E-mail address: lee-pf@ccmu.edu.cn (P. Li).

Peer review under the responsibility of Editorial Board of Intelligent Pharmacy.

https://doi.org/10.1016/j.ipha.2026.05.002
Received 17 April 2026; Received in revised form 8 May 2026; Accepted 10 May 2026
Available online 11 May 2026
2949-866X/© 2026 The Authors. Publishing services by Elsevier B.V. on behalf of Higher Education Press and KeAi Communications Co. Ltd. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

overweight (BMI 24–27.9), and obese (BMI > 28). 2) Disease and medication status: diagnosis, administered dose, steady-state plasma concentration, and concomitant medications. 3) Laboratory findings: alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (CREA), and CYP2D6 metabolic phenotype. The estimated glomerular filtration rate (eGFR) was calculated using the modified Schwartz formula for pediatric patients (aged < 18 years) and the EPI-CKD formula for adult patients (aged ≥ 18 years).

Inclusion criteria: Hospitalized patients who had received TDM for vortioxetine at our hospital.

Exclusion criteria: Incomplete baseline patient information; outpatients or specimens from other hospitals; patients whose vortioxetine plasma concentration had not reached steady state (less than 12 days since the last vortioxetine dosing regimen adjustment[4]); patients with severe hepatic impairment (defined as ALT or AST > 5 × upper limit of normal) or severe renal impairment (defined as eGFR < 30 mL/min/1.73 m^2); duplicate steady-state plasma concentration measurements from the same patient on the same dosing regimen; plasma concentrations below the lower limit of quantification of the assay method.

2.2. Blood sample collection and concentration determination

During continuous administration of vortioxetine hydrobromide tablets, 2 mL of fasting morning elbow venous blood was collected before drug intake. Serum was separated by centrifugation, and the steady-state plasma concentration of vortioxetine was determined using high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS). For patients with duplicate measurements under the same dosing regimen, only the last steady-state sample obtained during continuous medication was included in this study. The therapeutic reference range for vortioxetine plasma concentration adopted by our hospital is 10–40 ng·mL^{-1}, as recommended by the AGNP Consensus Guidelines.

Table 1
Distribution of vortioxetine serum concentration (n = 109).

Drug concentration (ng·mL^{-1})	n (%)	C (ng·mL^{-1})	C/D (ng·mL^{-1}·mg^{-1}·d)
< 10	19 (17.43%)	6.84 (4.93,8.00)	0.72 (0.49,1.26)
10~40	72 (66.06%)	22.50 (14.91,30.38)	1.48 (1.08,1.93)
> 40	18 (16.51%)	46.08 (42.01,53.09)	2.46 (2.15,2.84)
合计	109 (100%)	22.06 (13.26,35.34)	1.53 (0.97,2.23)

2.3. Statistical analysis

All statistical analyses were performed using SPSS version 23.0. Continuous variables were tested for normality using the Shapiro–Wilk test. Normally distributed variables were presented as mean ± standard deviation (X ± S), while non-normally distributed variables were presented as median (25th percentile, 75th percentile). Categorical variables were expressed as frequencies (percentages).

Comparisons of means between two independent groups with normally distributed data were performed using the independent-samples t-test, while the Mann–Whitney U test was used for non-normally distributed data. The Kruskal–Wallis H test was used to compare multiple groups of non-normally distributed data. If the overall difference was statistically significant, Mann–Whitney U test was used for post-hoc pairwise comparisons. Simple linear regression was employed to examine linear relationships between two continuous variables, and multiple linear regression was used to explore the effects of multiple independent variables on a continuous dependent variable. A two-sided p value < 0.05 was considered statistically significant.

3. Results

3.1. Baseline characteristics

During the study period, a total of 244 hospitalized patients underwent TDM for vortioxetine. After excluding 135 patients whose plasma concentrations had not reached steady state, 109 patients meeting the inclusion criteria were enrolled. The median age was 37.00 (19.00, 64.00) years, and the median BMI was 23.38 (21.24, 26.22) kg·m^{-2}. The median steady-state plasma concentration of vortioxetine was 22.06 (13.26, 35.34) ng·mL^{-1}. Among these patients, 19 had concentrations below 10 ng·mL^{-1}, 72 were within the therapeutic reference range, and 18 were above 40 ng·mL^{-1}. The median concentration/dose (C/D) ratio was 1.53 (0.97, 2.23) ng·mL^{-1}·mg^{-1}·d. The distribution of vortioxetine plasma concentrations is presented in Table 1.

3.2. Relationship between administered dose and steady-state plasma concentration

Simple linear regression analysis was performed between the steady-state plasma concentration of vortioxetine and the administered dose. The resulting linear regression equation was [vortioxetine] = 3.11 + 1.42 [doses] (R^2 = 0.263), indicating that the administered dose explained 26.3% of the variability in steady-state plasma concentration (see Fig. 1).

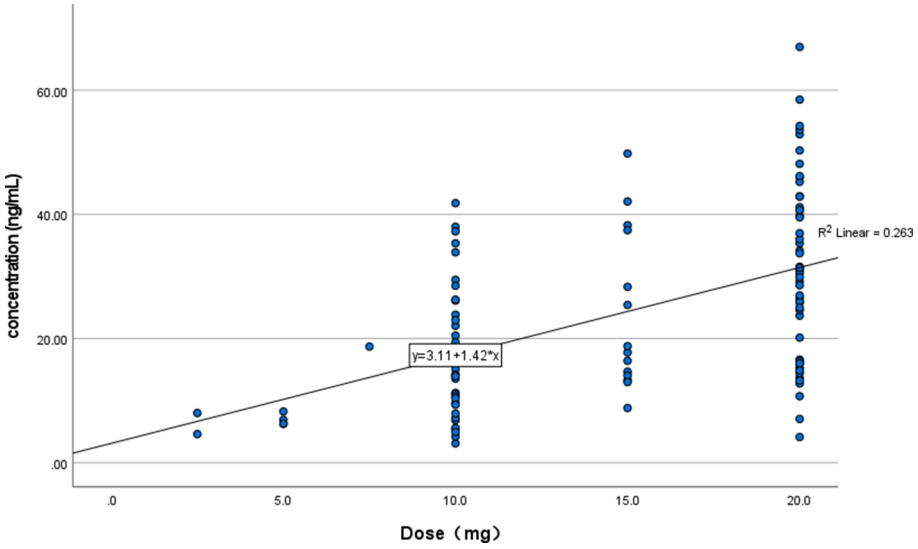


Fig. 1. Scatter plot of vortioxetine daily dose versus steady-state plasma concentration.

3.3. Effects of sex, age, BMI, eGFR, liver transaminases, CYP2D6 metabolic phenotype, and psychiatric concomitant medications on the C/D ratio

3.3.1. Effect of sex on the C/D ratio

A total of 40 male and 69 female patients were included in this study. The steady-state plasma concentrations and C/D ratios of the two groups are shown in Table 2. The Mann–Whitney *U* test showed no statistically significant difference in vortioxetine plasma concentrations between male and female patients ($p > 0.05$). The independent-samples *t*-test showed no statistically significant difference in the C/D ratio between the two groups ($p > 0.05$) (see Fig. 2).

Table 2
Effects of gender, age, BMI, eGFR and liver transaminase on the C/D of vortioxetine ($n = 109$).

Item	Category	*n* (%)	C (ng·mL^{-1})	C/D (ng·mL^{-1}·mg^{-1}·d)
Gender	Male	40 (36.70)	25.20 (15.96,34.04)	1.27 (0.80,1.85)
	Female	69 (63.30)	18.70 (10.71,36.16)	1.25 (0.57,1.21)
Age (year)	< 18	23 (21.10)	13.92 (6.29,29.20)	1.25 (0.68,2.06)
	18–60	54 (49.54)	25.89 (14.33,39.58)	1.70 (1.10,2.30)
	> 60	32 (29.36)	21.27 (14.07,31.30)	1.61 (1.07,2.17)
BMI (kg/m^2)	< 18.5	10 (9.17)	22.48 (12.34,35.71)	2.28 (1.22,2.68)
	18.5–24.0	54 (49.54)	24.75 (13.82,37.32)	1.57 (1.18,2.23)
	24.0–28.0	29 (26.61)	20.15 (11.74,34.74)	1.25 (0.77,1.91)
	> 28.0	16 (14.68)	17.47 (11.73,32.04)	1.30 (0.69,2.30)
eGFR	Normal	88 (80.73)	21.10 (13.06,35.34)	1.44 (0.93,2.19)
	Abnormal	21 (19.27)	22.95 (14.05,35.71)	1.71 (1.22,2.40)
Liver transaminase	Normal	90 (82.57)	20.32 (13.48,34.45)	1.27 (0.78,2.04)
	Abnormal	19 (17.43)	26.51 (11.07,38.00)	1.25 (0.66,1.80)

Note: Data are presented as median (interquartile range) for all variables, as the Shapiro–Wilk test indicated non-normal distribution for most continuous variables.

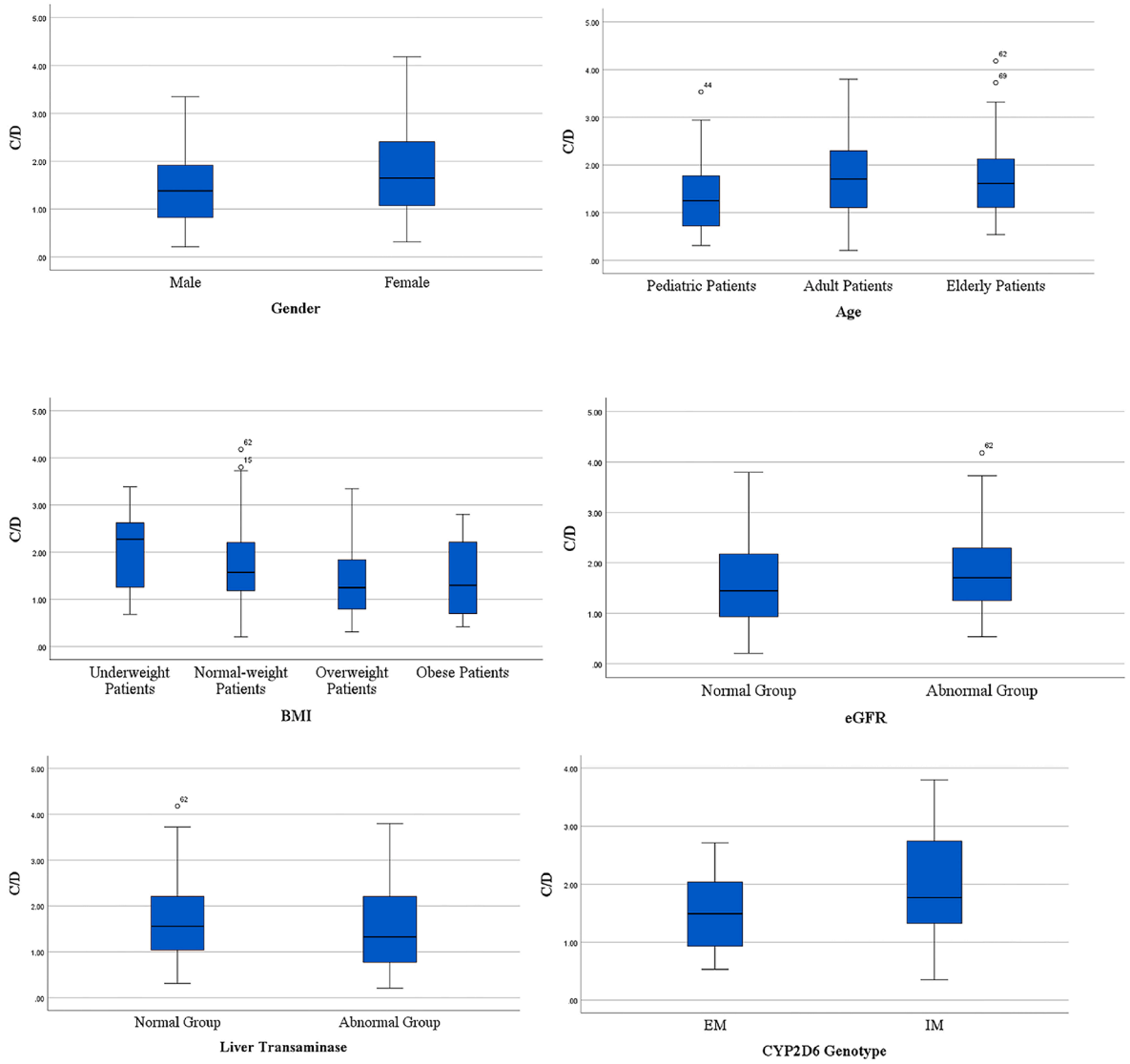


Fig. 2. Effects of gender, age, BMI, eGFR, liver transaminase and *CYP2D6* genotype on the C/D of vortioxetine.

Table 3
Effects of *CYP2D6* genotype on the C/D of vortioxetine ($n = 45$).

	Genotype	*n* (%)	C (ng·mL^{-1})	C/D (ng·mL^{-1}·mg^{-1}·d)
CYP2D6	EM	18 (40.00)	24.98 ± 14.35	1.53 ± 0.68
	IM	27 (60.00)	29.96 ± 15.30	2.02 ± 0.99

3.3.2. Effect of age on the C/D ratio

A total of 23 pediatric, 54 adult, and 32 elderly patients were included in this study. The steady-state plasma concentrations and C/D ratios of the three groups are shown in Table 2. Kruskal–Wallis H test showed no statistically significant differences in vortioxetine plasma concentrations or C/D ratios among the three age groups ($p > 0.05$) (see Fig. 2).

3.3.3. Effect of BMI on the C/D ratio

This study included 10 underweight, 54 normal-weight, 29 overweight, and 16 obese patients. The steady-state plasma concentrations and C/D ratios of the four groups are shown in Table 2. Kruskal–Wallis *H* test showed no statistically significant differences in vortioxetine steady-state plasma concentrations or C/D ratios among the four BMI groups ($p > 0.05$). Post-hoc pairwise comparisons also revealed no statistically significant differences in C/D ratios between any two BMI groups (all $p > 0.05$), including the comparison between underweight and obese groups ($p = 0.052$) (see Fig. 2).

3.3.4. Effect of eGFR on the C/D ratio

This study included 88 patients with normal renal function (eGFR ≥ 90 mL/min/1.73 m^2), with a median eGFR of 116.03 (102.21, 126.72) mL/min/1.73 m^2, and 21 patients with impaired renal function (eGFR 30–89 mL/min/1.73 m^2), with a median eGFR of 81.00 (61.81, 87.12) mL/min/1.73 m^2. The administered doses, steady-state plasma concentrations, and C/D ratios of the two groups are shown in Table 1. The Mann–Whitney *U* test showed no statistically significant differences in steady-state plasma concentrations or C/D ratios between patients with normal renal function and those with impaired renal function ($p > 0.05$) (see Fig. 2).

3.3.5. Effect of liver transaminase on the C/D ratio

This study included 90 patients with normal liver transaminase levels (ALT < 40 U/L and AST < 35 U/L) and 19 patients with elevated transaminase levels (ALT ≥ 40 U/L and/or AST ≥ 35 U/L,but both < 5 × upper limit of normal). The steady-state plasma concentrations and C/D ratios of the two groups are shown in Table 2. The Mann–Whitney *U* test showed no statistically significant difference in vortioxetine plasma concentrations between the normal and elevated transaminase groups ($p > 0.05$). The independent-samples *t*-test showed no statistically significant difference in the C/D ratio between the two groups ($p > 0.05$) (see Fig. 2).

3.3.6. Effect of CYP2D6 on the C/D ratio

Among the patients included in this study, 45 underwent pharmacogenomic testing. Of these, 18 patients had the *CYP2D6* extensive metabolizer (EM) genotype, and 27 had the intermediate metabolizer (IM) genotype. The steady-state plasma concentrations and C/D ratios of the two groups are shown in Table 3. According to the independent-samples *t*-test results, there were no statistically significant differences in steady-state plasma concentrations or C/D ratios between patients with *CYP2D6* EM and IM metabolic phenotypes ($p > 0.05$) (see Fig. 2).

3.3.7. Effects of psychiatric concomitant medications on the C/D ratio

The concomitant medications of the patients are shown in Table 4. Excluding sedative-hypnotics, the medications used by a relatively large number of patients (≥ 10 cases) included mirtazapine, quetiapine, olanzapine, aripiprazole, lithium carbonate, valproic acid, lamotrigine, and tandospirone. The Mann–Whitney *U* test results showed that concomitant use of lamotrigine had a statistically significant effect on the steady-state plasma concentration and C/D ratio of vortioxetine ($p < 0.05$), and concomitant use of lithium had a statistically significant effect on the steady-state plasma concentration of vortioxetine ($p < 0.05$). No other concomitant medications showed statistically significant effects on the steady-state plasma concentration or C/D ratio of vortioxetine ($p > 0.05$) (see Fig. 3).

3.4. Multiple linear regression analysis of factors influencing the vortioxetine C/D ratio

Multiple linear regression was used to explore the effects of sex, age, BMI, eGFR, liver transaminases, and psychiatric concomitant medications on the vortioxetine C/D ratio. The results showed no interactions among the factors. The inclusion of all variables in the regression equation was not statistically significant ($F = 1.302$, $p > 0.05$, $R^2 = 0.140$). The regression coefficients β for each independent variable are shown below (see Table 5).

4. Discussion

This study examined the effect of administered dose on steady-state plasma concentration using linear regression analysis. The results showed that the administered dose accounted for only 26.3% of the variability in steady-state plasma concentration, indicating that the factors influencing vortioxetine plasma concentrations are complex, with considerable interindividual variability. Therefore, TDM plays an important role in the individualized dosing of vortioxetine.

According to the AGNP consensus guidelines,[5] the reference range for the vortioxetine C/D ratio is 0.94–1.28. However, the C/D ratio observed in this study was 1.53 (0.97, 2.23), which is significantly higher than the reference range. This discrepancy may be attributed to

Table 4
Effects of drug combination on the C/D of vortioxetine ($n = 109$).

Drug name	Combination	*n* (%)	C (ng·mL^{-1})	C/D (ng·mL^{-1}·mg^{-1}·d)
Mirtazapine	Yes	13 (11.93)	28.33 (23.97,42.34)	1.89 (1.29,2.19)
	No	96 (88.07)	18.74 (13.04,34.08)	1.48 (0.94,2.28)
Quetiapine	Yes	31 (28.44)	18.23 (13.24,36.02)	1.50 (0.87,2.30)
	No	78 (71.56)	23.75 (13.63,35.34)	1.56 (1.03,2.22)
Olanzapine	Yes	11 (10.09)	31.41 (17.77,37.45)	1.99 (1.18,2.50)
	No	98 (89.91)	19.78 (12.38,34.45)	1.48 (0.95,2.18)
Aripiprazole	Yes	14 (12.84)	28.85 (14.40,32.39)	1.70 (1.00,2.68)
	No	95 (87.16)	19.40 (13.24,36.02)	1.50 (0.94,2.15)
Lithium	Yes	25 (22.94)	15.07 (9.36,26.24)	1.30 (0.86,1.85)
	No	84 (77.06)	25.20 (13.95,37.86)*	1.61 (1.02,2.29)
Valproic Acid	Yes	12 (11.01)	22.83 (10.60,36.20)	1.74 (1.35,2.54)
	No	97 (88.99)	22.06 (13.26,35.34)	1.50 (0.93,2.18)
Lamotrigine	Yes	10 (9.17)	10.28 (6.08,20.40)	1.03 (0.65,1.43)
	No	99 (90.83)	23.83 (14.04,36.02)**	1.57 (1.04,2.30)**

Note: *$p < 0.05$ compared with the concomitant lithium carbonate group; **$p < 0.05$ compared with the concomitant lamotrigine group.

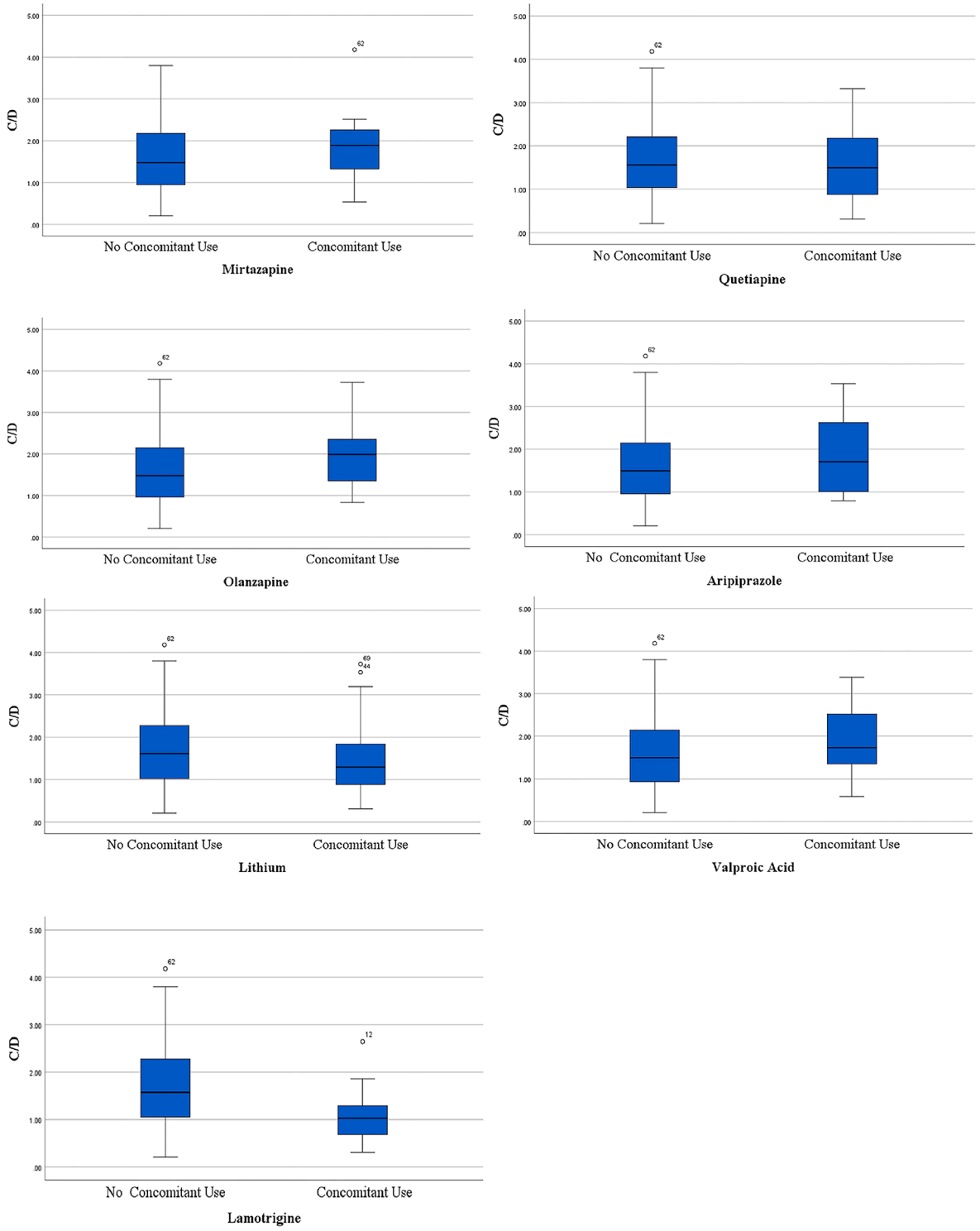


Fig. 3. Effects of drug combination on the C/D of vortioxetine.

inclusion of only Asian patients in this study, suggesting a potential racial or ethnic difference in the study sample. A study published in 2018 indicated that, considering a 50%–200% change in vortioxetine exposure as clinically meaningful, the effects of age, sex, race (specifically Black and White), body size, and hepatic or renal function on vortioxetine exposure were not clinically significant, and no dose adjustment of vortioxetine is required for these factors.[6] Similarly, the present study found no significant effects of age, sex, body size, or hepatic or renal function on the vortioxetine C/D ratio, suggesting that dose adjustment is also unnecessary under these circumstances in the Asian population.

Vortioxetine is primarily metabolized by the hepatic enzyme *CYP2D6*.[7] Frederiksen T et al.[8] found that vortioxetine plasma concentrations were 1.5 times higher in patients with the *CYP2D6* intermediate metabolizer (IM) phenotype compared to those with the extensive metabolizer (EM) phenotype. However, the present study did not observe a significant difference in the C/D ratio between CYP2D6 EM and IM patients. This discrepancy may be due to confounding effects from the inclusion of a large proportion of elderly and pediatric patients (accounting for 50.46% of the total sample) as well as the relatively

Table 5
Multiple linear regression analysis of influencing factors on the Cmin/D of vortioxetine.

Variables	Unstandardized coefficients		Standardized coefficients (β)	t	P
	B	Std error			
Gender	0.314	0.181	0.176	1.731	0.087
Age	−0.003	0.007	−0.071	−0.367	0.715
BMI	−0.021	0.021	−0.107	−1.001	0.320
eGFR	−0.005	0.006	−0.027	−0.264	0.792
Liver transaminase	−0.060	0.229	−0.159	−0.948	0.345
Mirtazapine	0.288	0.275	0.109	1.050	0.296
Quetiapine	−0.019	0.212	−0.010	−0.091	0.927
Olanzapine	0.313	0.296	0.110	1.057	0.293
Aripiprazole	0.199	0.275	0.078	0.723	0.471
Lithum	−0.147	0.221	−0.072	−0.666	0.507
Valproic Acid	0.089	0.297	−0.032	0.298	0.766
Lamotrigine	−0.464	0.322	−0.156	−1.438	0.154

small sample size of the pharmacogenomic subgroup.

One study has shown that vortioxetine combined with mood stabilizers can effectively improve clinical symptoms in patients with bipolar depression.[9] Lamotrigine is a first-line treatment for bipolar depression,[10] and concomitant use of these two agents is common in clinical practice. In the present study, univariate regression analysis revealed that concomitant use of lamotrigine might decrease the vortioxetine C/D ratio, whereas multivariate regression analysis did not identify a significant association, possibly due to insufficient sample size. After being metabolized by CYP2D6 and other enzymes, vortioxetine is conjugated with uridine diphosphate glucuronosyltransferase (UGT) and eliminated from the body.[11] One possible explanation for our observation is that lamotrigine might reduce vortioxetine plasma concentrations by inducing UGT-mediated metabolism, thereby decreasing the C/D ratio. However, this mechanistic hypothesis remains speculative, as direct enzymatic data are lacking in the current study. Further studies with dedicated drug-drug interaction designs are needed to confirm this potential mechanism. Additionally, no other clinical studies have reported an interaction between these two drugs. Whether their concomitant use reduces the antidepressant efficacy of vortioxetine requires validation through large-scale prospective studies.

The limitations of this study are as follows. First, as a retrospective observational study, selection bias may be present. For instance, hospitalized patients generally have relatively greater depression severity, which may limit the generalizability of the findings to outpatients or patients with mild-to-moderate depression. Second, the sample size was relatively small, limiting the statistical power of the study and affecting the general applicability of the results. Third, only patients with CYP2D6 EM and IM phenotypes were included; the study did not examine the effects of the UM (ultrarapid metabolizer) or PM (poor metabolizer) phenotypes on the vortioxetine C/D ratio. Finally, the study did not control for other information biases or confounding factors, such as the effects of diet (e.g., grapefruit juice), medication adherence, inflammatory status, smoking status or concomitant strong CYP2D6 inhibitors on vortioxetine plasma concentrations. Moreover, the pharmacogenomic subsample was relatively small ($n = 45$), which may have limited the statistical power to detect a true difference between EM and IM groups. Therefore, the lack of a significant difference in C/D ratios between these two phenotypes should be interpreted with caution, and a type II error cannot be ruled out. Fifth, the multiple linear regression model examining factors influencing the vortioxetine C/D ratio showed that the R^2 was only 0.140, and the result of the F-test was not statistically significant ($F = 1.302$, $p > 0.05$). This indicates that the variables included in the model (sex, age, BMI, eGFR, liver transaminases, and concomitant medications) collectively explained only a small fraction of the variability in the C/D ratio. This finding suggests that the factors influencing vortioxetine pharmacokinetics in this study remain largely unclear, and further investigation is needed to explore the effects of other influencing factors in the future, such as genetic polymorphisms beyond CYP2D6, inflammatory markers, or other patient-specific factors.

5. Conclusion

In summary, there is substantial interindividual variability in the pharmacokinetics of vortioxetine. The effect of concomitant lamotrigine on the vortioxetine C/D ratio requires further investigation and validation. Routine TDM is recommended for patients to ensure the safety and efficacy of vortioxetine treatment.

CRediT authorship contribution statement

Xiaoqian Lan: Writing – original draft, Methodology, Investigation, Conceptualization. **Hongyan Zhuang:** Writing – review & editing, Investigation. **Shuang Bao:** Investigation, Data curation. **Mengxi Niu:** Investigation, Data curation. **Yannan Zang:** Investigation. **Fei Jia:** Investigation. **Pengfei Li:** Writing – review & editing, Supervision, Resources, Funding acquisition, Conceptualization.

Data availability statement

The datasets generated and analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request for legitimate academic purposes.

Declaration of interest statement

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Acknowledgements

This work was supported by Beijing Municipal Administration of Hospitals (NO.YGLX202537).

References

1. Berardelli I, Rogante E, Formica F, et al. The efficacy of vortioxetine in the acute treatment of major depressive disorder: a systematic review and meta-analysis. *J Psychopharmacol.* 2025;39(2):92–105.
2. Adair M, Christensen MC, Florea I, et al. Vortioxetine in patients with major depressive disorder and high levels of anxiety symptoms: an updated analysis of efficacy and tolerability. *J Affect Disord.* 2023;328:345–354.
3. Verrienti G, Colonna I, Raccagni C. Use of vortioxetine in different neurological fields: a systematic review and future perspectives. *Neurol Sci.* 2025;46(5):2055–2071.
4. Lijing DAI, Yang Ye, Chen Yuqing, et al. Progress in individualized medication of novel antidepressant vortioxetine. *Pharm Today*. 2023;33(10):789–794.
5. Hiemke C, Baumann P, Bergemann N, et al. AGNP consensus guidelines for therapeutic drug monitoring in psychiatry:update 2011. *Pharmacopsychiatry*. 2011;44(6):195–235.
6. Chen G, Nomikos GG, Affinito J, et al. Effects of intrinsic factors on the clinical pharmacokinetics of vortioxetine. *Clin Pharmacol Drug Dev*. 2018;7(8):880–888.
7. Hiemke C, Bergemann N, Clement HW, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology:update 2017. *Pharmacopsychiatry*. 2018;51(1–02):9–62.
8. Frederiksen T, Smith RL, Jukic MM, et al. Association between CYP2D6 metabolizer status and vortioxetine exposure and treatment switching: a retrospective, naturalistic cohort study using therapeutic drug monitoring data from 640 patients. *J Clin Psychopharmacol.* 2022;42(4):396–399.
9. Siwek M, Chrobak AA, Sołtys Z, et al. A naturalistic, 24-week, open-label, add-on study of vortioxetine in bipolar depression. *Psychiatr Pol.* 2022;56(3):509–522.
10. Yatham LN, Kennedy SH, Parikh SV, et al. Canadian network for mood and anxiety treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) 2018 guidelines for the management of patients with bipolar disorder. *Bipolar Disord.* 2018;20(2):97–170.
11. Chen G, Højer AM, Areberg J, et al. Vortioxetine: clinical pharmacokinetics and drug interactions. *Clin Pharmacokinet.* 2018;57:673–686.