

ORIGINAL ARTICLE

Post-therapy plasma concentrations of quetiapine in Taiwanese patients

Cho-Yin Huang¹ | Yen-Feng Lin¹ | Chia-Ru Chen¹ | Shih-Ku Lin^{1,2} 

¹Department of Psychiatry, Taipei City Hospital and Psychiatric Center, Taipei, Taiwan

²Department of Psychiatry, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan

Correspondence

Shih-Ku Lin, Department of Psychiatry, Linkou Chang Gung Memorial Hospital, No.5, Fuxing St., Guishan Dist. Taoyuan 333, Taiwan.

Email: sklin@tpech.gov.tw

Funding information

Taipei City Government, Grant/Award Number: TCHIRB-10402102

Abstract

Aims: Quetiapine is widely used to treat psychiatric disorders such as major depression, generalized anxiety disorder, dysthymic disorder, and insomnia other than schizophrenia and bipolar disorder. This study investigated the diagnostic distribution of quetiapine use in patients in a psychiatric hospital, the doses of quetiapine prescribed, and the plasma concentrations (Cps) of quetiapine and active metabolites.

Methods: We enrolled 107 patients who had been prescribed quetiapine for at least 4 weeks. Diagnoses, demographics, and concomitant medications were recorded. Blood sampling was performed in the morning, approximately 12 h after the before-bed dose of quetiapine.

Results: Diagnoses comprised schizophrenia ($n = 25$), bipolar disorder ($n = 51$), major depression ($n = 15$), dysthymic disorder ($n = 9$), and others ($n = 7$). The daily dose (DD) of quetiapine ranged from 25 to 800 (175.9 ± 184.4) mg, with the mean Cp being 105.6 ± 215.3 ng/ml, with a mean Cps/DD ratio of 0.58 ± 0.55 ng/ml/mg. There was a moderate positive linear correlation between the dose and Cps of quetiapine ($r = 0.60$), and the interpatient variation in Cps/DD ratio was up to 26-fold.

Conclusion: Quetiapine is used in various doses to treat many psychiatric disorders other than psychosis, and it is usually prescribed as a secondary antipsychotic for symptoms such as insomnia or agitation. A wide interpatient variation of the Cps/DD ratio was noticed. Patients of East Asian descent may exhibit a 50% to 100% increase in the Cps/DD ratio for quetiapine compared with patients of Western descent.

KEYWORDS

bipolar disorder, quetiapine, racial difference, schizophrenia, therapeutic drug monitoring

1 | INTRODUCTION

Quetiapine is a second-generation antipsychotic used for the treatment of schizophrenia and bipolar disorder and as an adjunct treatment for major depressive disorder. Quetiapine has both immediate-release (IR) and extended-release (ER) forms. The recommended daily dose

(DD) of IR quetiapine for schizophrenia is 150–750mg, administered twice or thrice daily. The recommended DD of ER quetiapine is 400–800mg. Quetiapine is also approved for the treatment of bipolar mania as either monotherapy or adjunct therapy and for the treatment of bipolar depression as monotherapy, with the recommended DDs being 400–800 and 300–600mg, respectively. Additionally,

This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

© 2023 The Authors. *Neuropsychopharmacology Reports* published by John Wiley & Sons Australia, Ltd on behalf of The Japanese Society of Neuropsychopharmacology.

quetiapine has proven efficacious for treating major depression^{1,2} and generalized anxiety disorder.^{3,4} Nevertheless, the most common off-label use of quetiapine is for treating insomnia,⁵ with the typical DD range being 12.5–150 mg/day.

Quetiapine is metabolized primarily through hepatic metabolism by cytochrome P450 (CYP) 3A4⁶ and partially by the 2D6 system.⁷ DeVane and Nemeroff⁸ detailed the pharmacokinetics of quetiapine. In summary, food has minimal effects on quetiapine absorption, and smoking does not affect its pharmacokinetics. The elimination half-life of quetiapine is approximately 7 h, and 11 metabolites formed through hepatic oxidation have been identified. The inactive sulfoxide metabolite and the parent acid metabolite accounted for 15.1% and 14.7%, respectively, and the two active metabolites 7-hydroxyquetiapine (7-OH-quetiapine) and 7-hydroxy-N-desalkylquetiapine (7-OH-N-desquetiapine) constitute approximately 5% and 2% of the parent compound quetiapine, respectively. The suggested therapeutic Cps of quetiapine for schizophrenia range from 100 to 500 ng/ml, and N-desquetiapine 100 to 250 ng/ml.⁹

Both the pharmacokinetic and pharmacodynamic properties of a drug can affect the clinical response to an illness. In the treatment of schizophrenia, the blood levels of antipsychotics may affect the corresponding clinical responses, and these levels can be influenced by several individual factors, including medication adherence, body weight (BW) or body mass index, smoking habit, sex, individual genetic differences in the cytochrome P450 system, and the effect of drug–drug interaction. For example, the interpatient variation of Cps of clozapine was up to 12-fold in a group of 62 patients who took the DD dose of 400 mg,¹⁰ and up to 10-fold in a group of 88 patients who took the DD of haloperidol 20 mg.¹¹

The aim of this study was to investigate the diagnostic distribution and prescribed dosages of quetiapine in patients at a psychiatric hospital and to monitor the Cps of quetiapine and its active metabolites 7-OH-quetiapine and 7-OH-N-desquetiapine in these patients to explore the interpatient variations in Cps/DD.

2 | METHODS

2.1 | Patients

Patients aged between 20 and 65 years from Taipei City Hospital, who were prescribed quetiapine were included after obtaining written informed consent. To ensure steady-state Cps, changing the dose of quetiapine within 2 weeks was excluded. The patients' diagnoses, demographics, and concomitant medications were recorded. This study was supported by the Taipei City Government (TCHIRB-10402102).

2.2 | Quetiapine assay

Blood samples were taken in the morning, approximately 12 h after the dosing of quetiapine. From each patient, venous blood

samples (10 ml) were collected into K2EDTA-containing tubes (BD, Plymouth, UK). The plasma quetiapine samples were analyzed through ultra-performance liquid chromatography–tandem mass spectrometry (UPLC-MS/MS; Waters, Milford, MA, USA). Chromatographic separation was performed on an Acquity UPLC BEH C18 column (1.7 μ m; 2.1 \times 50 mm; Waters) equipped with an Acquity UPLC BEH C18 VanGuard Pre-column (1.7 μ m; 2.1 \times 5 mm; Waters). The mass spectrometer was a triple quadrupole Xevo TQ MS system (Waters). In the experiments, we utilized an electrospray ionization source in positive-ionization mode. Chromatographic conditions were set as follows: a flow rate of 0.3 ml/min with a mobile phase composed of 10 mM ammonium formate buffer (pH 3.0; solution A) and MeOH (solution B). The gradient program started at an initial mixture of 84% solution A with 16% solution B. Solution B was increased to 47% at 6.0 min and then increased to 95% at 7.5 min and held for 0.5 min. MassLynx software (version 4.1; Waters) was used for data processing. The lower limit of quantification was 0.2 ng/ml. The interday and intraday precisions by relative standard deviation for quetiapine, 7-OH-quetiapine and 7-OH-N-desquetiapine were 0.6%–5.0% and 1.1%–4.5%, 0.3%–5.4% and 1.0%–8.0%, and 0.7%–10.0% and 1.1%–4.4%, respectively.

2.3 | Data analysis

SPSS software (version 20; IBM, Armonk, NY, USA) was used for all statistical data analyses in this study. Statistical significance was set at $p < 0.05$.

3 | RESULTS

This study enrolled 107 patients (male patients: 51; mean age: 51.9 ± 13.0 years; mean body weight: 66.3 ± 13.3 kg). The sample comprised patients with schizophrenia ($n = 25$), bipolar disorder ($n = 53$), major depression ($n = 15$), dysthymic disorder ($n = 9$), and others ($n = 7$). Table 1 compares DD, Cps, and Cps/DD ratio in different diagnoses. There were 59 (55%) patients received the IR form, and 48 patients received the ER form of quetiapine.

The DDs of quetiapine ranged from 25 to 800 mg, with a mean value of 175.9 ± 184.4 mg. The mean Cp of quetiapine was 105.6 ± 215.3 ng/ml, and the Cps of 7-OH-quetiapine and 7-OH-N-desquetiapine were 4.1 ± 6.5 (3.9%) and 4.6 ± 5.1 ng/ml (4.4%), respectively. Figure 1 illustrates the plot of quetiapine dose and Cps of quetiapine, 7-OH-quetiapine, and 7-OH-N-desquetiapine. The Pearson correlation coefficients (r) between the DD and Cps of quetiapine, 7-OH- and 7-OH-N-desquetiapine were 0.60, 0.76, and 0.86, respectively. In addition, the inter-individual pharmacokinetic variability of quetiapine—derived as the fold difference between the 5th and 95th percentiles of the Cps/DD ratio—was up to 26-fold. For 7-OH-quetiapine and 7-OH-N-desquetiapine, the variations were up to 10 folds and

TABLE 1 Dose of quetiapine, plasma concentrations of quetiapine, and metabolites between different diagnoses

Diagnosis	n (%)	Dose (mg)	Cps of QT (ng/ml)	Cps/DD (ng/ml/mg)	Cps of 7-OH-QT (ng/ml)	7-OH-N-des QT (ng/ml)
Schizophrenia	25 (23)	218.4 ± 195.7	178.9 ± 366.1	0.60 ± 0.52	6.1 ± 9.8	6.0 ± 6.3
Bipolar disorder	51 (48)	228.4 ± 202.4	115.7 ± 160.6	0.55 ± 0.58	5.2 ± 6.0	5.6 ± 5.4
Major depression	15 (14)	50.0 ± 46.3	30.5 ± 32.8	0.68 ± 0.42	0.8 ± 0.5	1.2 ± 0.5
Dysthymic disorder	9 (8)	30.6 ± 11.0	15.7 ± 16.9	0.57 ± 0.69	0.6 ± 0.3	1.1 ± 0.4
Others	7 (7)	128.6 ± 134.2	85.7 ± 142.3	0.53 ± 0.49	3.2 ± 3.6	3.0 ± 2.9
Total	107 (100)	175.9 ± 184.4	105.6 ± 215.3	0.58 ± 0.55	4.1 ± 6.5	4.6 ± 5.1

Abbreviations: Cps, plasma concentration; DD, daily dose; N-des, N-desalkyl; QT, quetiapine.

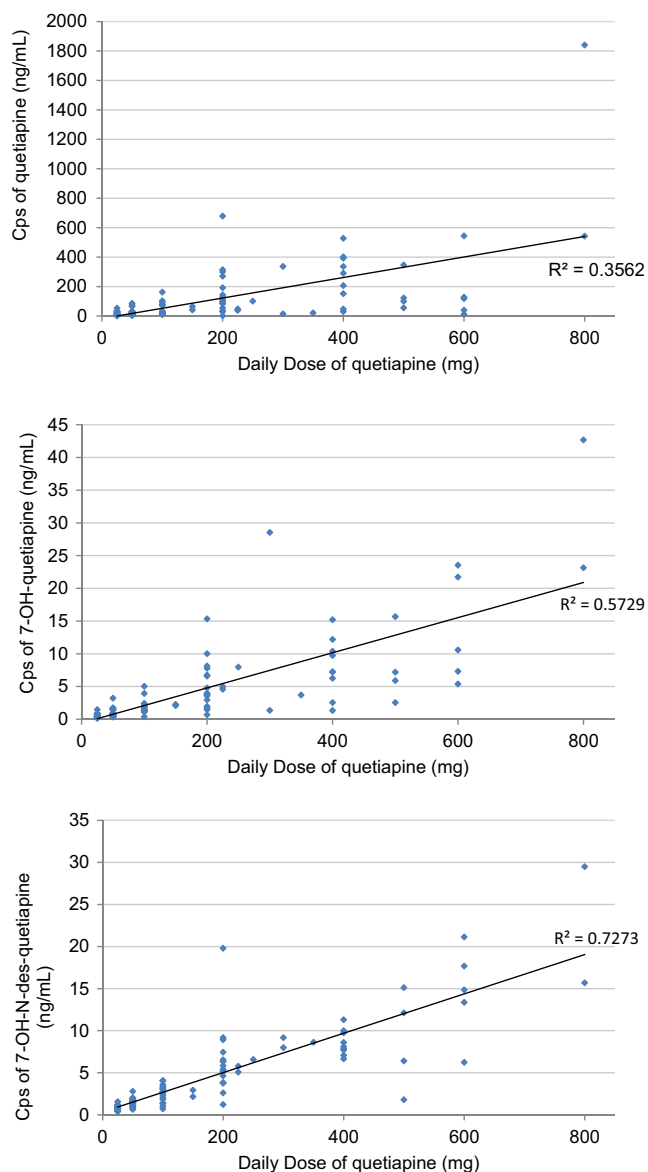


FIGURE 1 Plot of quetiapine dose and plasma concentrations (cps) of quetiapine, 7-OH-quetiapine, and 7-OH-N-des quetiapine

25 folds, respectively. Male patients received a slightly higher DD of quetiapine than female patients did (200.0 ± 209.2 vs. 154.0 ± 157.2 mg, $p = 0.199$), but no difference in the Cps/DD

ratio (0.63 ± 0.62 vs. 0.53 ± 0.46 ng/ml/mg, $p = 0.356$) was observed between sex. The mean Cps/DD ratio derived for quetiapine was 0.58 ± 0.55 ng/ml/mg.

Quetiapine was prescribed concomitantly with carbamazepine, a strong CYP 3A4 inducer,¹² in five patients; the mean DD was 285.0 ± 231.5 mg, and the Cp and Cps/DD ratio were 14.7 ± 10.3 ng/ml and 0.07 ± 0.05 ng/ml/mg, respectively. Moreover, quetiapine was prescribed concomitantly with lamotrigine in five patients; the mean DD was 60.0 ± 22.5 mg, and the Cp and Cps/DD ratio were 15.4 ± 9.2 ng/ml and 0.29 ± 0.20 ng/ml/mg, respectively. Besides, 30 patients were prescribed concomitantly with valproic acid, with mean DD, Cps, and Cps/DD ratio as 266 ± 225.5 mg, 234.2 ± 354.3 ng/ml, and 0.79 ± 0.72 ng/ml/mg.

Table 2 presents a comparison of the numbers of, DDs prescribed for, Cps determined, and Cps/DD ratio between patients taking IR and ER form quetiapine. Higher doses were used in ER form, resulting in higher Cps of quetiapine. The Cps/DD in ER quetiapine was higher than that derived for IR quetiapine by approximately 44% after dosing for about 12 h ($p < 0.05$).

4 | DISCUSSION

Quetiapine is widely prescribed for many psychiatric disorders.¹³ The recommended DD of quetiapine for schizophrenia treatment is 150–750 mg; however, in clinical practice, many patients receive polypharmacy (two or more types of antipsychotics). In our sample of 25 patients with schizophrenia, 19 (mean DD: 150.0 mg) received an additional antipsychotic, and only six were treated with monotherapy (mean DD: 433.3 mg). The suggested range of therapeutic Cps for quetiapine is 100 to 500 ng/ml⁹; in our six patients who received monotherapy, the mean Cp was 456.3 ng/ml, which was within the suggested range.

Quetiapine is usually prescribed as a secondary antipsychotic for other symptoms such as insomnia or agitation. A comparison of the association of antipsychotic polypharmacy versus monotherapy with psychiatric rehospitalization conducted by Tiihonen et al.¹⁴ revealed that quetiapine monotherapy was associated with the least successful rate, while low-dose quetiapine combined with other antipsychotics was commonly prescribed with moderate effects.

TABLE 2 Mean \pm SD of dose, cps, and cps/DD ratio of immediate release (IR) and extended release (ER) quetiapine

Dosage form	n (%)	Dose (mg)	Cps (ng/ml)	Cps/DD (ng/ml/mg)
IR	59 (55)	78.4 \pm 68.3	30.1 \pm 31.2	0.48 \pm 0.42
ER	48 (45)	198.5 \pm 295.6	198.5 \pm 295.8	0.69 \pm 0.65

Quetiapine was most commonly prescribed for bipolar disorder (recommended DD: 400–800 mg) in our sample ($n = 51\%$, 49%). Most patients with bipolar disorder received quetiapine (mean DD: 229.2 mg) as an add-on medication to mood stabilizers (valproic acid [$n = 25$], lithium [$n = 10$], carbamazepine [$n = 5$], and lamotrigine [$n = 5$]; total: 88%). A higher dose of quetiapine was prescribed for bipolar mania and mixed type (DD: 262.8 \pm 208.0 mg, $n = 41$) than for bipolar depression (DD: 85.0 \pm 47.4 mg, $n = 10$). None of the patients in the bipolar group received quetiapine as monotherapy.

A study by Castberg et al.¹⁵ on the interactions of quetiapine with other drugs suggested that comedication with carbamazepine would significantly reduce Cps by 86%. In our sample, the mean Cps/DD ratio was 0.07 \pm 0.05 ng/ml/mg in patients who were prescribed concomitantly carbamazepine. Carbamazepine is a strong CYP3A4 inducer, and coadministration of carbamazepine could decrease the Cps of quetiapine by increasing its clearance to 7.5-fold.¹⁶ A study by Andersson et al.¹⁷ reported that the Cps/DD of quetiapine was around 58% lower in the lamotrigine group than in the control group, and suggested that induction of quetiapine glucuronidation by lamotrigine might be the reason for this decreasing effect. In our sample, the mean Cps/DD ratio was 0.29 \pm 0.20 ng/ml/mg in patients who were prescribed concomitantly lamotrigine. Although valproic acid is a weak CYP 3A4 inhibitor,¹⁸ Aichhorn et al.¹⁹ reported that co-medicated with valproic acid was associated with a 77% increase in quetiapine plasma levels. In our samples, the relative % of quetiapine Cps/DD ratio to the whole group (0.58 ng/ml/mg) of concomitant use of carbamazepine, lamotrigine and valproic acid were -87%, -45%, and +36%, respectively. Based on these findings, we agree with the aforementioned report and recommend that drug–drug interaction is an important clinical issue when prescribing quetiapine. Concomitant use of quetiapine with carbamazepine, and lamotrigine would decrease, and with valproic acid would increase the Cps of quetiapine.

The third group in our sample comprised major depression ($n = 16$). All patients in this group were treated with antidepressants and a low dose of quetiapine (mean DD: 50.0 mg). This small dose regimen was also administered to the fourth group of patients with dysthymia ($n = 9$, mean DD: 30.6 mg), indicating that the hypnotic–sedative effect was the major target in these two groups. Quetiapine is widely used off-label as a treatment for insomnia.^{5,20} A clinical guideline for the management of insomnia suggests that quetiapine should be used only in patients who have a comorbid psychiatric disorder as opposed to primary insomnia.²¹ Insomnia is one of the common symptoms of major depression and dysthymia; therefore, the concomitant use of low-dose quetiapine can ameliorate sleep disturbance, and the metabolite N-des quetiapine can improve depressive mood.²²

Bakken et al.²³ ever monitored the Cps/DD ratio of quetiapine in 927 serum samples from 601 patients and reported a 15-fold interpatient variation, while Hasselström & Linnet²⁴ reported a 238-fold variation in a group of 62 patients. The interpatient variation of the present study was 26-fold. These large interpatient variations in the Cps of quetiapine might be due to the abovementioned factors, and also the drug–drug interaction might play a significant role since polypharmacy was popular in the study patients.

Male were prescribed higher doses of quetiapine compared with female. However, we observed no significant differences in analyte Cps/DD between males and females. These results are similar to those reported in the literature by Fisher et al.²⁵ and Bakken et al.,²³ in which both studies indicated that sex difference does not play a major role in the metabolism of quetiapine.

Quetiapine is metabolized primarily by the CYP 3A4 enzyme and partially by the CYP 2D6 enzyme. Both enzymes demonstrate different metabolic activities depending on racial characteristics,^{26–28} and they exhibit relatively poor metabolic activities in patients of East Asian heritage. For example, for haloperidol, also metabolized primarily by the CYP 3A4 enzyme and partially by the CYP 2D6 enzyme, the Cps associated with the metabolic activities of these enzymes differed significantly between races, which is much higher in East Asian subjects.^{29,30} A study conducted in Austria by Aichhorn et al.¹⁹ reported the mean Cps/DD ratio derived for quetiapine (all IR) was 0.144 \pm 0.016 in 36 males and 0.195 \pm 0.017 in 58 females. We calculated the mean Cps/DD ratio as 0.18 ng/ml/mg. A study conducted in the United Kingdom by Fisher et al.²⁵ reported a mean Cp of quetiapine (IR or ER) as 195 ng/ml in 99 samples from 59 patients with a median DD 600 mg, yielding a Cps/DD ratio of approximately 0.33 ng/ml/mg. A study conducted in Norway by Bakken et al.²³ reported that the mean Cps/DD ratio derived for quetiapine (all IR) in 927 samples collected from 601 patients was 0.56 nmol/L/mg (0.21 ng/ml). Another study from the United Kingdom by Handley et al.³¹ used therapeutic drug monitoring (TDM) data for 946 quetiapine samples (IR or ER) collected from 487 patients. The study revealed that the DD of quetiapine was 401–600 mg in 124 patients and 601–800 mg in 126 patients, with the corresponding mean Cps being 215 and 296 ng/ml, respectively. Based on these dose ranges, we calculated the mean Cps/DD ratio in these two groups was approximately 0.42 ng/ml/mg. A study in Denmark by Hasselström & Linnet²⁴ also used TDM data for 62 patients and revealed a median Cps/DD ratio of 0.41 nmol/L/mg (0.16 ng/ml/mg) for quetiapine (all IR). Ostad Haji et al.³² reported the mean Cps/DD ratio of quetiapine (43 IR) as 0.34 \pm 0.24 ng/ml/mg in 105 depressive patients by the mean DD of 222 \pm 125 mg.

A study in China by Li et al.³³ used TDM data for 21 patients who were prescribed a fixed dose of 200 mg quetiapine (all IR) twice

TABLE 3 Comparison of published data of quetiapine daily dose, plasma concentration and plasma concentration/daily dose

Authors/country	Patient number (IR/ER)	Mean/median DD (mg)	Mean cps (ng/ml)	Mean cps/DD (ng/ml/mg)
Aichhorn et al. ¹⁹ /Austria	94 (IR)	381 (mean)	68 (mean)	0.18 (mean)
Hasselstrøm and Linnet ²⁴ /Denmark	62 (IR)	400 (median)	66 (median)	0.16 (mean)
Bakken et al. ²³ /Norway	601 (IR)	500 (median)	104 (median)	0.21 (median)
Fisher et al. ²⁵ /UK	59 (IR or ER)	600 (median)	195 (mean)	0.33 (mean)
Handley et al. ³¹ /UK	487 (IR or ER)	600 (median)	242 (mean)	0.42 (mean)
Ostad Haji et al. ³² /Germany	105 (43/62)	222 (mean)	46 (mean)	0.34 (mean)
Li et al. ³³ /China	21 (IR)	400 (fixed dose)	147 (mean)	0.37 (mean)
Li et al. ³⁴ /China	40 (ER)	572 (mean)	365 (mean)	0.64 (mean)
Present study/Taiwan	107 (59/48)	176 (mean)	106 (mean)	0.58 (mean)

Abbreviations: DD, daily dose; ER, extended release; IR, Immediate release.

daily. The mean steady-state Cp of quetiapine was 147 ± 142 ng/ml, and the mean Cps/DD ratio was 0.37 ng/ml/mg. Another study in China by Li et al.³⁴ monitored the Cps of quetiapine (all ER) in patients who were prescribed DDs of 300 mg ($n = 13$), 600 mg ($n = 13$), and 800 mg ($n = 14$), revealing the Cps as 212, 320, and 551 ng/ml, respectively. The mean Cps/DD ratio of quetiapine for the whole sample was 0.64 ng/ml/mg. In the present study, the mean Cps/DD ratio of quetiapine (59 IR and 48 ER) was 0.58 ng/ml/mg. After comparing the results of these studies, we determined that patients of Chinese heritage may have approximately 50% to 100% higher Cps/DD ratio (0.37–0.64 ng/ml/mg) of quetiapine than Caucasian patients (0.16–0.42 ng/ml/mg). Table 3 summarizes the published data of quetiapine DD, Cps, and Cps/DD from different countries.

Higher Cps in Oriental patients have also been reported for clozapine, a substrate of CYP 1A2 and 2C19,^{10,35} aripiprazole, a substrate of CYP2D6 and 3A4,³⁶ and lurasidone, a substrate of CYP 3A4.³⁷ These differences have been observed among different racial populations. For example, Shimada et al.³⁸ compared the CYP enzymes in the liver microsomes including CYP 1A2, 2A6, 2B6, 2C, 2D6, 2E1, and 3A between Japanese and Caucasians and found the total CYP content was higher in Caucasian than in Japanese populations. McGraw and Waller³⁹ have reviewed the CYP450 variations in different ethnic populations including CYP1A2, 2C8, 2C9, 2C19, 2D6, 3A4, and 3A5 single nucleotide polymorphisms (SNPs), and suggested that racial/ethnic differences in metabolic phenotype can be explained by differences in SNP distribution.

We compared the Cps and Cps/DD ratio of IR and ER quetiapine (Table 2). Our results indicate that ER quetiapine (200 and 50 mg) was more frequently prescribed to patients with schizophrenia or bipolar disorder compared with IR quetiapine (100 and 25 mg). We also observed that the Cps/DD ratio derived for ER quetiapine was higher than that derived for IR quetiapine by approximately 44% after dosing for about 12 h ($p < 0.05$). The study by Fisher et al.²⁵ also reported this finding. A study by Figueroa et al.⁴⁰ reported that the least squares mean of the ratio of the area under the plasma concentration-time curve over a 24 h dosing interval for ER and IR quetiapine was 1.04 (0.92–1.19), suggesting similar bioequivalence between the IR and ER forms.

The limitations of the present study are the small sample size, the convenience sampling method, and concerns about medication adherence. Because quetiapine is widely used in clinical practice for off-label purposes, most patients in our sample were not within the recommended dose range indicated for the treatment of schizophrenia and bipolar disorder.³¹ Nevertheless, our results reflect the real-world prescription of quetiapine. Another limitation was that we did not measure the active metabolite of N-desalkylquetiapine, and did not perform a well-controlled or head-to-head comparison of racial differences in the Cps/DD ratio for quetiapine; therefore, our findings warrant further verification.

In conclusion, although quetiapine is categorized as an antipsychotic, it is widely used to treat many psychiatric disorders other than psychosis at various doses, and a wide interpatient variation of the Cps/DD ratio was noticed. Based on our comparison of Asian and Western studies, we believe that individuals of East Asian descent may exhibit a 50% to 100% increase in the Cps/DD ratio for quetiapine compared with patients of Western descent.

AUTHOR CONTRIBUTIONS

CYH and SKL designed this project. CYH, YFL, CRC, and SKL recruited participants and collected blood samples, and findings were interpreted by all the authors. SKL prepared the first draft, which was revised by all authors. All authors approved the final manuscript.

ACKNOWLEDGMENT

This study was supported by the Taipei City Government. The authors thank Mr. Yan-Lung Chiou for assistance with data management. This manuscript was edited by Wallace Academic Editing.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Under the restriction of the Human Subject Committee of Taipei City Hospital, the data supporting this study's findings are available on request from the corresponding author on a reasonable basis, via an application for approval from the Human Subject Committee.

ETHICS STATEMENT

This study was approved by the Human Subject Committee of Taipei City Hospital (TCHIRB-10402102).

INFORMED CONSENT

Every participant gave written informed consent after receiving the study explanation.

ORCID

Shih-Ku Lin  <https://orcid.org/0000-0002-5123-0389>

REFERENCES

- Weisler R, Joyce M, McGill L, Lazarus A, Szamosi J, Eriksson H. Extended release quetiapine fumarate monotherapy for major depressive disorder: results of a double-blind, randomized, placebo-controlled study. *CNS Spectr*. 2009;14:299–313.
- Bortnick B, el-Khalili N, Banov M, Adson D, Datto C, Raines S, et al. Efficacy and tolerability of extended release quetiapine fumarate (quetiapine XR) monotherapy in major depressive disorder: a placebo-controlled, randomized study. *J Affect Disord*. 2011;128:83–94.
- Bandelow B, Chouinard G, Bobes J, Ahokas A, Eggens I, Liu S, et al. Extended-release quetiapine fumarate (quetiapine XR): a once-daily monotherapy effective in generalized anxiety disorder. Data from a randomized, double-blind, placebo- and active-controlled study. *Int J Neuropsychopharmacol*. 2010;13:305–20.
- Katzman MA, Brawman-Mintzer O, Reyes EB, Olausson B, Liu S, Eriksson H. Extended release quetiapine fumarate (quetiapine XR) monotherapy as maintenance treatment for generalized anxiety disorder: a long-term, randomized, placebo-controlled trial. *Int Clin Psychopharmacol*. 2011;26:11–24.
- Anderson SL, Vande Griend JP. Quetiapine for insomnia: a review of the literature. *Am J Health Syst Pharm*. 2014;71:394–402.
- Nemeroff CB, Kinkead B, Goldstein J. Quetiapine: preclinical studies, pharmacokinetics, drug interactions, and dosing. *J Clin Psychiatry*. 2002;63(Suppl 13):5–11.
- Le Daré B, Ferron PJ, Allard PM, Clément B, Morel I, Gicquel T. New insights into quetiapine metabolism using molecular networking. *Sci Rep*. 2020;10:19921.
- DeVane CL, Nemeroff CB. Clinical pharmacokinetics of quetiapine: an atypical antipsychotic. *Clin Pharmacokinet*. 2001;40:509–22.
- Hiemke C, Bergemann N, Clement HW, Conca A, Deckert J, Domschke K, et al. Consensus guidelines for therapeutic drug monitoring in neuropsychopharmacology: update 2017. *Pharmacopsychiatry*. 2018;51:e1.
- Chang WH, Lin SK, Lane HY, Hu WH, Jann MW, Lin HN. Clozapine dosages and plasma drug concentrations. *J Formos Med Assoc*. 1997;96:599–605.
- Lane HY, Lin HN, Hwu HG, Jann M, Hu WH, Chang WH. Haloperidol plasma concentrations in Taiwanese psychiatric patients. *J Formos Med Assoc*. 1995;94:671–8.
- Spina E, Pisani F, Perucca E. Clinically significant pharmacokinetic drug interactions with carbamazepine. An update. *Clin Pharmacokinet*. 1996;31:198–214.
- Zhornitsky S, Potvin S, Motesafi H, Dubreucq S, Rompré PP, Stip E. Dose-response and comparative efficacy and tolerability of quetiapine across psychiatric disorders: a systematic review of the placebo-controlled monotherapy and add-on trials. *Int Clin Psychopharmacol*. 2011;26:183–92.
- Tiihonen J, Taipale H, Mehtälä J, Vattulainen P, Correll CU, Tanskanen A. Association of Antipsychotic Polypharmacy vs monotherapy with psychiatric rehospitalization among adults with schizophrenia. *JAMA Psychiat*. 2019;76:499–507.
- Castberg I, Skogvoll E, Spigset O. Quetiapine and drug interactions: evidence from a routine therapeutic drug monitoring service. *J Clin Psychiatry*. 2007;68:1540–5.
- Grimm SW, Richtand NM, Winter HR, Stams KR, Reece SB. Effects of cytochrome P450 3A modulators ketoconazole and carbamazepine on quetiapine pharmacokinetics. *Br J Clin Pharmacol*. 2006;61:58–69.
- Andersson ML, Björkhem-Bergman L, Lindh JD. Possible drug-drug interaction between quetiapine and lamotrigine—evidence from a Swedish TDM database. *Br J Clin Pharmacol*. 2011;72:153–6.
- Wen X, Wang JS, Kivistö KT, Neuvonen PJ, Backman JT. In vitro evaluation of valproic acid as an inhibitor of human cytochrome P450 isoforms: preferential inhibition of cytochrome P450 2C9 (CYP2C9). *Br J Clin Pharmacol*. 2001;52:547–53.
- Aichhorn W, Marksteiner J, Walch T, Zernig G, Saria A, Kemmler G. Influence of age, gender, body weight and valproate comedication on quetiapine plasma concentrations. *Int Clin Psychopharmacol*. 2006;21:81–5.
- Wiegand MH, Landry F, Brückner T, Pohl C, Veselý Z, Jahn T. Quetiapine in primary insomnia: a pilot study. *Psychopharmacology*. 2008;196:337–8.
- Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. *J Clin Sleep Med*. 2008;4:487–504.
- Jensen NH, Rodriguiz RM, Caron MG, Wetsel WC, Rothman RB, Roth BL. N-desalkylquetiapine, a potent norepinephrine reuptake inhibitor and partial 5-HT_{1A} agonist, as a putative mediator of quetiapine's antidepressant activity. *Neuropsychopharmacology*. 2008;33:2303–12.
- Bakken GV, Rudberg I, Molden E, Refsum H, Hermann M. Pharmacokinetic variability of quetiapine and the active metabolite N-desalkylquetiapine in psychiatric patients. *Ther Drug Monit*. 2011;33:222–6.
- Hasselstrøm J, Linnet K. Quetiapine serum concentrations in psychiatric patients: the influence of comedication. *Ther Drug Monit*. 2004;26:486–91.
- Fisher DS, Handley SA, Flanagan RJ, Taylor DM. Plasma concentrations of quetiapine, N-desalkylquetiapine, o-desalkylquetiapine, 7-hydroxyquetiapine, and quetiapine sulfoxide in relation to quetiapine dose, formulation, and other factors. *Ther Drug Monit*. 2012;34:415–21.
- Hsieh KP, Lin YY, Cheng CL, Lai ML, Lin MS, Siest JP, et al. Novel mutations of CYP3A4 in Chinese. *Drug Metab Dispos*. 2001;29:268–73.
- Yamaori S, Yamazaki H, Iwano S, Kiyotani K, Matsumura K, Saito T, et al. Ethnic differences between Japanese and Caucasians in the expression levels of mRNAs for CYP3A4, CYP3A5 and CYP3A7: lack of co-regulation of the expression of CYP3A in Japanese livers. *Xenobiotica*. 2005;35:69–83.
- Liou YH, Lin CT, Wu YJ, Wu LS. The high prevalence of the poor and ultrarapid metabolite alleles of CYP2D6, CYP2C9, CYP2C19, CYP3A4, and CYP3A5 in Taiwanese population. *J Hum Genet*. 2006;51:857–63.
- Potkin SG, Shen Y, Pardes H, Phelps BH, Zhou D, Shu L, et al. Haloperidol concentrations elevated in Chinese patients. *Psychiatry Res*. 1984;12:167–72.
- Jann MW, Chang WH, Lam YW, Hwu HG, Lin HN, Chen H, et al. Comparison of haloperidol and reduced haloperidol plasma levels in four different ethnic populations. *Prog Neuro-Psychopharmacol Biol Psychiatry*. 1992;16:193–202.
- Handley SA, Bowskill SV, Patel MX, Flanagan RJ. Plasma quetiapine in relation to prescribed dose and other factors: data from a therapeutic drug monitoring service, 2000–2011. *Ther Adv Psychopharmacol*. 2013;3:129–37.
- Ostad Haji E, Wagner S, Fric M, Laux G, Pittermann P, Röschke J, et al. Quetiapine and norquetiapine serum concentrations and clinical effects in depressed patients under augmentation therapy with quetiapine. *Ther Drug Monit*. 2013;35:539–45.



33. Li KY, Li X, Cheng ZN, Peng WX, Zhang BK, Li HD. Multiple dose pharmacokinetics of quetiapine and some of its metabolites in Chinese suffering from schizophrenia. *Acta Pharmacol Sin.* 2004;25:390–4.
34. Li Q, Su YA, Liu Y, Chen JX, Tan YL, Yang FD, et al. Pharmacokinetics and tolerability of extended-release quetiapine fumarate in Han Chinese patients with schizophrenia. *Clin Pharmacokinet.* 2014;53:455–65.
35. de Leon J, Rajkumar AP, Kaithi AR, Schoetsanitis G, Kane JM, Wang CY, et al. Do Asian patients require only half of the clozapine dose prescribed for Caucasians? A critical overview. *Indian J Psychol Med.* 2020;42:4–10.
36. Lin SK, Chen CK, Liu YL. Aripiprazole and dehydroaripiprazole plasma concentrations and clinical responses in patients with schizophrenia. *J Clin Psychopharmacol.* 2011;31:758–62.
37. Huang CY, Lin SK. Therapeutic drug monitoring of lurasidone. *Psychiatry Clin Neurosci.* 2022;76:674–5.
38. Shimada T, Yamazaki H, Mimura M, Inui Y, Guengerich FP. Interindividual variations in human liver cytochrome P-450 enzymes involved in the oxidation of drugs, carcinogens and toxic chemicals: studies with liver microsomes of 30 Japanese and 30 Caucasians. *J Pharmacol Exp Ther.* 1994;270:414–23.
39. McGraw J, Waller D. Cytochrome P450 variations in different ethnic populations. *Expert Opin Drug Metab Toxicol.* 2012;8:371–82.
40. Figueroa C, Brecher M, Hamer-Maansson JE, Winter H. Pharmacokinetic profiles of extended release quetiapine fumarate compared with quetiapine immediate release. *Prog Neuro-Psychopharmacol Biol Psychiatry.* 2009;33:199–204.

How to cite this article: Huang C-Y, Lin Y-F, Chen C-R, Lin S-K. Post-therapy plasma concentrations of quetiapine in Taiwanese patients. *Neuropsychopharmacol Rep.* 2023;43:50–56. <https://doi.org/10.1002/npr2.12303>