Supplementary Information

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Insights into the Population Pharmacokinetics and Pharmacodynamics of Quetiapine: A Systematic Review

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Table S1. The description of operational criteria for each of the items

Items	Suggested contents
Title/abstract	
Name of the drug(s) studied	The abstract includes the name of the drug(s) studied;
Population studied	The abstract includes population in whom it was studied;
Primary objective	The abstract includes the results of the primary objective;
Major findings	The abstract includes the major clinical pharmacokinetic findings;
Background	
Pharmacokinetic data	Pharmacokinetic data (i.e. absorption, distribution, metabolism, excretion) that are known and relevant to the drugs being studied are described;
Study rationale	An explanation of the study rationale is provided;
Methods	
Eligibility criteria	Eligibility criteria of study participants are described;
Co-administration or food	Co-administration (or lack) of study drug(s) with other potentially interacting drugs or food within this study is described
Dosing	Drug preparation and administration characteristics, including dose or frequency are described;
Formulation	Drug preparation and administration characteristics, including formulation or route are described;
Sampling schedule	Body fluid or tissue sampling (timing, frequency, and storage) for quantitative drug measurement are described
Bioanalytical methods	Validation of quantitative bioanalytical methods used in the study are referenced or described if applicable
Methods for handling missing data	Methods for handling missing data such as drug concentrations below the LLOQ should also be described.
Modeling software	Pharmacokinetic modeling software used is described
Statistical methods and software	Statistical methods, including software used, are described
Candidate structural models	Pharmacokinetic modeling methods used is described, including assumptions made regarding the number of compartments and order of kinetics (zero, first, or mixed order)
Residual error structure	The assumptions of the distributions of the residual error structure (e.g. additive, proportional, etc.) Should be described;
Methods for base model determination	The structural model determinate should be justified on the grounds of biology, drug mechanism, prior literature, etc.
Methods for base model evaluation	Standard goodness-of-fit plots were generated to evaluate the base model, such as observed concentrations versus population and individual predictions, histograms of subject-specific random effects, visual predictive checks, etc.
Covariates analysis strategy	Covariates incorporated into pharmacokinetic models are identified and described

Table S1 (continued)

Methods for final model evaluation	Standard goodness-of-fit plots were generated to evaluate the base model, such as observed concentrations versus population and individual predictions, histograms of subject-specific random effects, visual predictive checks (vpcs), etc.
Distribution of individual model parameters	The assumptions of the distributions of individual model parameters (e.g. lognormal) should be described;
Estimation method(s) used	Pharmacokinetic modeling estimation method used is described, such as FOCE-I.
Results	
Population characteristic	A table of summary clinical variables of subjects;
No. of subjects and observations	A table of summary statistics of subject demographics;
Schematic of the final model	A schematic of the final structural model to characterize the drug absorption, distribution and elimination for complicate model
Table of the final model parameters	All final model parameter estimates should be listed in a table.
Final model evaluation plots	Including observed concentrations versus population and individual predictions, histograms of subject-specific random effects, visual predictive checks (vpcs), etc.
Summary of the model-building process and the derived final model	Including the results from the best base model, univariate covariate analysis, covariate selection (pivotal steps) and the final model
Plot of concentrations vs. Time and/or effects vs. Concentrations	A plot of drug concentrations versus time in all subjects is displayed to understand choices for candidate structural models;
Discussion/conclusion	
Study limitations	Study limitations describing potential sources of bias and imprecision, where relevant, should be described;
Study findings	The relevance of study findings (applicability, external validity) is described;

Abbreviations: LLOQ, lower limit of quantitation; FOCE-I, first-order conditional estimation method with the interaction.

Table S2. Search Strategies

PUBMED (Inception to March 31, 2023), Total: 93		
1	Quetiapine	5891
2	Seroquel	5930
3	ICI 204,636	3191
4	ICI-204636	3187
5	ICI204636	3187
6	ICI 204636	3187
7	1 or 2 or 3 or 4 or 5 or 6	5931
8	population pharmacokinetic	38004
9	population pharmacokinetic / pharmacodynamic	29050
10	pharmacokinetic model	146056
11	nonlinear mixed effect model	5284
12	NONMEM	2812
13	WinNonMix	11
14	P-PHARM	58
15	NLMIXED	111
16	NLME	221
17	MONOLIX	203
18	MwPHARM	30
19	Pmetrics	144
20	USC*PACK	30
21	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	170879
22	7 and 21 (121) limited to human (95) published in English (119)	93

Table S2 (continued)

EMBASE (Inception to March 31, 2023), Total: 168		
1	Quetiapine	28289
2	Seroquel	1777
3	ICI 204,636	29
4	ICI-204636	63
5	ICI204636	2
6	ICI 204636	63
7	1 or 2 or 3 or 4 or 5 or 6	28309
8	population pharmacokinetic*	51918
9	population pharmacokinetic and pharmacodynamic*	6607
10	Pharmacokinetic* model*	177736
11	nonlinear mixed effect model*	3911
12	NONMEM	5202
13	WinNonMix	16
14	P-PHARM	85
15	NLMIXED	133
16	NLME	883
17	MONOLIX	476
18	MwPHARM	78
19	Pmetrics	238
20	USC*PACK	26
21	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	211703
22	7 and 21 (494) limited to human (438) limited to article (206)	168

Table S2 (continued)

WEB OF SCIENCE (Inception to March 31, 2023), Total:170		
1	Quetiapine	11337
2	Seroquel	521
3	ICI 204,636	81
4	ICI-204636	15
5	ICI204636	0
6	ICI 204636	15
7	1 or 2 or 3 or 4 or 5 or 6	11526
8	population pharmacokinetic*	47824
9	population pharmacokinetic and pharmacodynamic*	14634
10	Pharmacokinetic* model*	174058
11	nonlinear mixed effect model*	14435
12	NONMEM	4102
13	WinNonMix	13
14	P-PHARM	56
15	NLMIXED	210
16	NLME	431
17	MONOLIX	251
18	MwPHARM	28
19	Pmetrics	154
20	USC*PACK	14
21	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20	213909
22	7 and 21 (228) exclude animal (192) limited to article (211) published in English (223)	170

Table S3. List of tested and significant covariates in the included models

Study (Publication year)	Ref	Tested covariates	Selection criteria		Selected covariates		
			Forward inclusion[f]	Backward elimination[f]	CL/F	V/F	F
Kimko et al. (2000)	[12]	Age, BW, sex	NR		/	/	/
Isbister et al. (2007)	[43]	Age, sex, co-activated charcoal, CYP3A4 strong inducer[a], moderate/weak inhibitor[b] and substrate	NA[g]		co-CYP3A4 strong inducer	/	co-activated charcoal
Bigos et al. 2010)	[39]	Age, BW, sex, race, co-bupropion and other medication[c], smoking status	P < 0.001	NR	co-bupropioneh	BW	/
Shilbayeh et al. (2015)	[45]	Age, body mass index, quetiapine formulation, CYP3A5 (s776746) genotype, ABCB1 (3435CC) genotype, smoking status	P < 0.05	P < 0.01	/	/	/
Zhou et al. (2015)	[44]	Age, BW, race, sex, alanine aminotransferase, aspartate aminotransferase, bilirubin	P < 0.05	P < 0.001	Age	/	/
Glatard et al. (2019)	[40]	Age, BW, quetiapine formulation, sex, BAGE, DAGE, genetic polymorphism of CYP3A4 (rs4646437, rs2740574, rs35599367 i.e CYP3A4*22), CYP3A5 (rs776746), ABCB1 (rs1128503, rs9282564) and POR (rs1057868), albuminemia, co-strong/moderate inducer[d], CYP3A4 strong/moderate/weak inhibitor[e], permeability-glycoprotein inhibitors, lithium and grapefruit juice	P < 0.05	P < 0.008	CYP3A4 (rs35599367) genotype, co-CYP3A4 inhibitor and strong/moderate inducer	/	/
Fukushi et al. (2020)	[46]	Age, BW, sex, γ-GTP, alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin, platelets, protein	P < 0.05	P < 0.01	γ-GTP	BW	/

Abbreviations: BAGE, baseline age; BW, body weight; CL/F, apparent clearance of quetiapine; co, co-administration; DAGE, the age difference from the first concentration to each concentration; F, bioavailability; NA, not applicable; NR, not reported; Ref, reference; V/F, apparent central volume of distribution; γ-GTP, γ-glutamyl transpeptidase.

[a]Strong CYP3A4 inducer is carbamazepine.

[b]Moderate CYP3A4 inhibitor is fluoxetine; weak CYP3A4 inhibitors is fluvoxamine.

[c]Specific medication was not identified.

[d]Strong CYP3A4 inducers were phenytoin, metamizole and carbamazepine; moderate CYP3A4 inducers were oxcarbazepine, bosentan and etravirine.

[e]Strong CYP3A4 inhibitors were amiodarone, atazanavir, darunavir, diltiazem and ritonavir; moderate CYP3A4 inducers were desogestrel, clobazam, fluoxetine and nifedipine; weak CYP3A4 inhibitors was ranitidine.

[f]If the stepwise selection procedure is not implemented, then these aspects should be disregarded.

[g]Clinically significant difference was regarded as a 20% difference in a parameter value.

[h]Significant on CL/F but the magnitude of the effect was not reported.

Table S4. Simulated quetiapine level based on the included models*.

			IR QTP 400mg QD			IR QTP 200mg BID			ER QTP 400 mg QD			IR QTP 4000 mg single dose	
Compound	**Model**	**Ref**	**$C_{min, ss}$**	**$C_{max, ss}$**	**$AUC_{24, ss}$**	**$C_{min, ss}$**	**$C_{max, ss}$**	**$AUC_{24, ss}$**	**$C_{min, ss}$**	**$C_{max, ss}$**	**$AUC_{24, ss}$**	**C_{min}**	**AUC_{24}**
QTP	Kimko et al. (2000)	[12]	12.5	858.2	5438.7	40.8	480.8	5427.5	/	/	/	/	/
	Isbister et al. (2007)	[43]	/	/	/	/	/	/	/	/	/	323.5	44323.5
	Catafau et al. (2008)	[41]	3.3	/	4230.3	30.2	/	3972.4	/	/	/	/	/
	Bigos et al. (2010)	[39]	15.9	/	3818.8	57.5	/	3803.8	/	/	/	/	/
	Shilbayeh et al. (2015)	[45]	4.4	776.8	4073.0	33.9	429.8	3865.03	/	/	/	/	/
	Zhou et al. (2015)	[44]	39.5	592.7	5668.1	106.5	376.9	5551.7	76.2	398.9	5684.0	/	/
	Korell et al. (2018)	[42]	19.0	492.1	3394.9	54.3	282.5	3387.0	28.4	347.2	3386.2	/	/
	Glatard et al. (2019)	[40]	23.9	/	3490.8	62.6	/	3657.8	66.6	/	3696.5	/	/
	Fukushi et al. (2020)	[46]	/	/	/	/	/	/	27.7	/	4561.3	/	/
	Median		15.9	684.8	4073.0	54.3	403.4	3865.0	47.5	373.1	4128.9	/	/
QTP-suf	Korell et al. (2018)	[42]	22.0	571.0	3923.2	64.2	325.8	3915.5	32.6	399.6	3914.0	/	/
Nor-QTP	Glatard et al. (2019)	[40]	47.7	433.4	4697.0	101.1	276.8	4507.6	105.6	266.2	4689.0	/	/

*Data was simulated based on the reference models and standard virtual patients (40-year-old adult males with a body weight of 70 kg, a cytochrome P450 3A4*1/*1 genotype, and a γ-glutamyl transpeptidase value of 19 U/L), $C_{max, ss}$ value was not available for studies employed limited sampling strategy.

Abbreviations: $AUC_{24,}$ area under the quetiapine plasma concentration-time curve from time zero to 24 hours (ng·h/mL); $AUC_{24, ss}$, steady state area under the plasma concentration-time curve from time zero to 24 hours (ng·h/mL); BID, twice daily, $C_{max, ss}$, steady state peak plasma concentration (ng/mL); C_{min}, through plasma concentration, sampled at 24 hours after dose (ng/mL); $C_{min, ss}$, steady state through plasma concentration (ng/mL); ER, extended-release form of quetiapine; IR, immediate-release form of quetiapine; nor-QTP, N-desalkylquetiapine; QD, once daily; QTP, quetiapine; QTP-suf, quetiapine-fumarate; Ref, reference.