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BRIEF REPORT

Exploring the Prevalence of Clozapine Phenotypic Poor Metabolizers in 4 Asian Samples: They Ranged Between 2 and 13%

Can-Jun Ruan, Ph.D.;[$] Chuan-Yue Wang, M.D., Ph.D.;[%] Yi-Lang Tang, M.D., Ph.D.;[%*] Shih-Ku Lin, M.D.;[#] Seung-Tae Lee, M.D., Ph.D.;[=] Kyung Sue Hong, M.D., Ph.D.;[+] Anto P. Rajkumar, M.D.;[-,@] Kuruthukulangara S. Jacob, M.D., Ph.D.;[-] Jose de Leon, M.D.[&]

[$]Laboratory of Clinical Psychopharmacology & The National Clinical Research Centre for Mental Disorders & Beijing Key Lab of Mental Disorders, Beijing Anding Hospital, Capital Medical University, Beijing, China.

[%]Department of Psychiatry, The National Clinical Research Centre for Mental Disorders & Beijing Key Lab of Mental Disorders & Beijing Institute for Brain Disorders Center of Schizophrenia, Beijing Anding Hospital, Capital Medical University, Beijing, China.

[*]Department of Psychiatry and Behavioral Sciences, Emory University School of Medicine, Atlanta, GA, USA.

[#]Department of General Psychiatry, Taipei City, Psychiatric Center, Taipei, Taiwan, and Department of Psychiatry, School of Medicine, Taipei Medical University, Taipei, Taiwan.

[=]Department of Laboratory Medicine, Yonsei University College of Medicine, Seoul, Korea

[+]Department of Psychiatry, Sungkyunkwan University School of Medicine, Samsung Medical

Center, Seoul, Korea.

[-]Department of Psychiatry, Christian Medical College, Vellore, India.

[@]Department of Old Age Psychiatry, Institute of Psychiatry, Psychology, & Neuroscience, King's College London, London, United Kingdom and Institute of Mental Health, Jubilee Campus, University of Nottingham, Triumph Road, Nottingham, United Kingdom.

[&]Mental Health Research Center, Eastern State Hospital, Lexington, KY, USA, and Psychiatry and Neurosciences Research Group (CTS-549), Institute of Neurosciences, University of Granada, Granada, Spain, and Biomedical Research Centre in Mental Health Net (CIBERSAM), Santiago Apóstol Hospital, University of the Basque Country, Vitoria, Spain.

Correspondence: Jose de Leon, M.D., Room 3A15A, Mental Health Research Center, Eastern State Hospital, 1350 Bull Lea Road, Lexington, KY 40511, USA e-mail: jdeleon@uky.edu

Phone (1-859) 246-8440; Fax (1-859) 246-8446

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Can-Jun Ruan: rcjjenny@msn.com http://orcid.org/0000-0002-1625-7367

Chuan-Yue Wang: wang.cy@163.net https://orcid.org/0000-0001-6549-3713

Yi-Lang Tang: ytang5@emory.edu http://orcid.org/0000-0003-0958-7904

Shih-Ku Lin: DAF68@tpech.gov.tw http://orcid.org/0000-0002-5123-0389

Seung-Tae Lee: LEE.ST@yuhs.ac http://orcid.org/0000-0003-1047-1415

Kyung Sue Hong: hongks@skku.edu http://orcid.org/0000-0002-1250-6151

Anto P. Rajkumar: anto.rajamani@kcl.ac.uk http://orcid.org/0000-0003-3203-6326

Kuruthukulangara S. Jacob: as ksjacob1959@gmail.com http://orcid.org/0000-0001-7728-8071

Jose de Leon: jdeleon@uky.edu http://orcid.org/0000-0002-7756-2314

ABSTRACT

Purpose/Background: Clozapine clearance is influenced by sex, smoking status, ethnicity, co-prescription of inducers or inhibitors, obesity and inflammation. In 126 Beijing inpatients, we measured repeated trough steady-state serum concentrations and identified 4% (5/126) who were phenotypical poor metabolizers (PMs); none were ultrarapid metabolizers (UMs). They were defined as being 2 standard deviations beyond the means of total clozapine concentration/dose ratios stratified by sex and smoking. Using this definition, this study explores the prevalences of PMs and UMs using data from 4 already-published Asian samples. Three samples were East Asian (Beijing 2, Taipei and Seoul); one was from South India (Vallore). **Findings/Results:** The prevalence of phenotypical PMs ranged from 2-13%, but inflammation was not excluded. The prevalence was 7.3% (14/191) for Beijing 2, 11% (8/70) for Taipei, 13% (9/67) for Seoul, and 2% (2/101) for the Vellore sample. Five phenotypical PMs appeared to be associated with extreme obesity. Phenotypic UM prevalence ranged from 0-1.6%, but may be partly explained by lack of adherence. A Vellore phenotypic UM appeared to be associated with induction through high coffee intake. **Implications/Conclusions:** Around 10% of Asians may be clozapine PMs and may only need 50-150 mg/day to get therapeutic concentrations. Future studies combining gene sequencing for new alleles with repeated concentrations and careful control of confounders including inhibitors, inflammation and obesity should provide better estimations of the prevalence of phenotypic clozapine PMs across races. Clozapine UM studies require excluding potent inducers, careful supervision of compliance in inpatient settings and multiple serum concentrations.

Key words: Asian continental ancestry group/genetics**;** clozapine, blood; clozapine, pharmacokinetics; CYP1A2; India; sex; smoking.

Introduction

Clozapine is mainly metabolized by the cytochrome 1A2 (CYP1A2).[1] The clearance of CYP1A2 drugs is lower in females and higher in smokers.[2] Therefore, after stratification by smoking and sex in four groups, female non-smokers have the lowest clozapine clearance and male smokers the highest. In 2007, in a very well-controlled study, using caffeine as a probe for CYP1A2 activity, Ghotbi et al.[2] demonstrated that after smoking and sex stratification Koreans have lower activity than Caucasian Swedes.

There is a linear relationship between clozapine dose (D) in mg/day and concentration (C) (ng/ml). This linear relationship can be represented by the concentration-to-dose (C/D) ratio, which is measured in ng/ml per mg/day. The C/D ratio is a measure of drug clearance, which is influenced by genetic, personal and environmental factors.[3] In 1994, Jerling et al.[4] demonstrated that carbamazepine, an inducer, decreases clozapine C/D ratio while fluvoxamine, an inhibitor, increases it. When comparing different individuals, a very low clozapine C/D ratio indicates an ultrarapid metabolizer (UM) phenotype while a very high C/D ratio indicates a poor metabolizer (PM) phenotype.[3] While the clozapine C/D ratio can be used by clinicians for dosing, the total clozapine C/D ratio, which is calculated by adding clozapine and norclozapine, reflects clozapine metabolism more comprehensively and is a better measure of clozapine clearance.[3,5]

People from Chine, Korea, Japan and Mongolia, who are closely related from the genetic point of view, are usually called East Asians.[6] In 1996, two studies showed that Chinese had concentrations similar to Caucasians with half the clozapine dosage.[7,8] In 1998, a shrewd Pakistani[9] clinician reported that Pakistani psychiatrists also used doses similar to those used by Chinese psychiatrists and proposed that Pakistanis also have lower clozapine clearance than Caucasians, but similar to Chinese. This is not surprising since the Food and Drug

Administration (FDA), based on genetic proximity, define Asian ethnicity[6] as referring to people originating geographically from Pakistan to Japan. The first clozapine comparison of Asians and Caucasians was done by Ng et al.[10] who found that 20 Singaporean Asians (from 3 ethnicities: Chinese, Indians and Malayans) had higher clozapine C/D ratios than 20 Australian Caucasians. Clozapine doses in East Asians appear to be much lower than in Western countries.[11] Other Asian counties may also use lower clozapine doses than Western countries. An Indian survey[12] of 117 psychiatrists reported that almost all (86%) of their patients got stabilized on clozapine doses lower than 300 mg/day. A recent Asian survey[13] described average clozapine doses ranging from 58 to 368 mg/day in samples from several countries with no published therapeutic drug monitoring data (TDM).

Based on clinical experience, a review article in 2015[3] proposed that in United States (US) Caucasians, the average schizophrenia patient usually needs from 300 (female non-smokers) to 600 mg/day (male smokers) to reach the lowest part of the clozapine therapeutic range (350 ng/ml) with respective C/D ratios of 1.20 to 0.60. Based on the limited published data on Chinese patients[7,8] and linear kinetics, it was proposed that East Asians may have clozapine C/D ratios that are twice as large, ranging from 1.20 to 2.40, which means that they need only half the clozapine dosage of US Caucasians.[3] A 2019 systematic review supported that conclusion,[11] since the clozapine C/D ratio was higher when comparing weighted mean values of 1.57 in 876 East Asians and 1.07 in 1147 Caucasians ($p<.001$). Similarly, the total clozapine C/D ratio was higher when comparing weighted mean values of 2.30 in 876 East Asians and 1.86 in 717 Caucasians ($p=.009$).

CYP1A2 known alleles have no clear effects on function[15] and no frequent null alleles have been described. A unique French clozapine PM had a very rare allele, CYP1A2*7 in

heterozygous state,[16] which has never again been reported. This patient demonstrated a total clozapine C/D ratio of 6.85. Her clozapine C/D ratio was 4.32, indicating that a clozapine dose of 81 mg/day would be enough to achieve a serum concentration of 350 ng/ml. In a Beijing sample,[11] which we are going to call Beijing Sample 1, 129 Chinese inpatients (>95% Han) received repeated TDM measures, after carefully controlling for confounding by inflammation and inhibitors. Means stratified by sex and smoking were calculated and clozapine phenotypic PMs were defined as those at 2 standard deviations (SDs) above their respective mean total clozapine C/D ratios (Supplementary Table S1). Using this criterion, 4% (5/126) were identified as phenotypical PMs who did not have CYP1A2*7.[14] The clozapine phenotypic PMs had clozapine C/D ratios ranging from 3.60 to 6.08, indicating that doses from 75 to 115 mg/day would be enough to provide them with a serum concentration of at least 350 ng/ml.[11]

In Beijing Sample 1,[11] no clozapine phenotypic UMs were identified after defining UMs as those who fell 2 SDs lower than the mean clozapine C/D ratio of their group after stratification by sex and smoking status (Supplemental Table S1). However, one female non-smoker had a normal clozapine C/D ratio of 1.78. After taking carbamazepine, an inducer of clozapine metabolism, her clozapine clearance was reduced to 0.79, placing her close to the phenotypic UM range that would require a clozapine dose of 443 mg/day to reach a concentration of at least 350 ng/ml. That is a very high dose for an East Asian female non-smoker, who would typically require a dose of 150 mg/day.[11]

For studying clozapine PMs and UMs, it is necessary to consider phenoconversion, the phenomenon that converts genotypically normal metabolizers into phenotypic PMs or UMs. Several inhibitors of clozapine metabolism can lead to phenotypic clozapine PM status. Fluvoxamine is a potent clozapine inhibitor[17] and its effects are very strong since it decreases

clozapine clearance by a factor of 0.1 to 0.2.[18] Ciprofloxacin (and some other members of its family) are clozapine inhibitors. Valproate can also be a clozapine inhibitor in some patients.[18] Oral contraceptives can be clinically relevant inhibitors of clozapine metabolism; in fact, it is believed that the inhibitory effect of estrogens can explain why females tend to have lower CYP1A2 activity than males. In general, any drug that behaves as a clinically relevant inhibitor of clozapine metabolism may lead to a phenotypic PM status; such cases have been described with phenothiazines, tricyclic antidepressants and even high doses of sertraline.[18] Severe infections or inflammations, by releasing cytokines[5] that inhibit CYP1A2 and other CYPs, may also lead to phenotypic clozapine PM status. A US double-blind study with multiple measures and a well-controlled environment suggested that clozapine may deposit in fat tissue and that obesity may be associated with lower clozapine clearance. This led to the hypothesis that extremely obese patients could be phenotypic PMs.[19] In Western countries, clozapine UMs have been described due to: 1) unknown genetic variations,[20] 2) taking potent inducers, such as carbamazepine or phenytoin, and 3) in an unusual patient, valproate combined with smoking appeared to act as a potent inducer.[21]

In summary, Beijing Sample 1 with 126 carefully studied inpatients with a mean of 9 TDMs, provided a prevalence of 4% PMs and no UMs after excluding the carbamazepine patient. Using the PM and UM definitions from Beijing Sample 1, we explore, in this study, the prevalence of phenotypic PMs and UMs in four Asian samples.[22-25] Three were from East Asians[22-24] and one was from South Indians.[25]

Methods

Definitions of phenotypic clozapine PMs and UMs

Supplemental Table S1 provides the values for mean total C/D ratio ± > 2 SDs from the mean of each group, stratified by sex and smoking, thus defining phenotypic clozapine PMs and UMs. The less reliable definitions for phenotypic PMs and UMs, which use clozapine C/D ratios, were also provided because the Indian sample[25] measured only clozapine.

Beijing Sample 2

Between 1999 and 2002, at a Beijing hospital, Tang et al.[22] studied 193 inpatients who were Chinese, most of them probably of Han ethnicity, with single trough steady-state concentrations measured by high-performance liquid chromatography (HPLC) with ultraviolet detection (UV). After eliminating 2 patients with missing norclozapine concentrations, we analyzed 191 patients (Supplemental Table S2). This sample provided data on body mass indexes (BMIs).

Taipei sample

In 2004 at a Taipei hospital, Lin et al.[23] studied 102 Chinese outpatients with single trough steady-state concentrations measured by HPLC with UV detection. After eliminating 17 patients (9 in which sex was not specified, 1 who was taking carbamazepine and 7 who were taking fluvoxamine), we analyzed 85 patients (Supplemental Table S2). This sample included weights but not BMI data.

Seoul sample

In 2007 at a Seoul hospital, Lee et al.[24]studied 78 Korean outpatients with single trough steady-state concentrations measured by HPLC and tandem mass spectrometry. After eliminating 11 patients with missing data, we analyzed 67 patients (Supplemental Table S2). This sample included weights but not BMI data.

Vellore sample

In 2009 at a Vellore hospital, Rajkumar et al.[25] studied 101 South Indians, most of whom were outpatients, with single trough steady-state concentrations only of clozapine, measured by HPLC with UV detection. No patient was taking carbamazepine, fluvoxamine or oral contraceptives. Patients co-medicated (N=9) with fluoxetine or sertraline (usually mild inhibitors) and valproate (usually a mild inhibitor or inducer) were included (Supplemental Table S2). This sample included BMI data.

Results

Total clozapine C/D ratios, and doses needed to reach 350 ng/ml in these four samples, were similar to the means in Beijing Sample 1 for total samples (Supplemental Table S3) and for the samples stratified by smoking and sex (Supplemental Table S4). Thus, it is reasonable to use Beijing Sample 1 to define clozapine PMs and UMs in the four new Asian samples.

Prevalence of clozapine PMs in 4 new Asian samples

Supplemental Table S5 describes phenotypic PMs. Supplemental Table S6 describes PMs for which an explanation could not be found. However, none of the four new studies investigated inflammation/infection at the time of blood collection.

In Beijing Sample 2 we found 2 phenotypic clozapine PMs, probably due to extreme obesity in 2 female non-smokers (Supplemental Table S5). Then, we identified 7.3% (14/191) as potential PMs needing from 34 to 128 mg/day to get a therapeutic concentration of at least 350 ng/ml (Table Supplemental S6).

In the Taipei sample, we found 11% (8/70) who were potentially clozapine PMs needing from 41 to 161 mg/day to reach a therapeutic concentration of at least 350 ng/ml (Supplemental Table S6). Our definition of clozapine PMs would work well if it identifies patients on

fluvoxamine. Thus, it was reassuring that 6 of 9 excluded patients (67%) on fluvoxamine were phenotypic clozapine PMs (Supplemental Table S5, footnote b).

In the Seoul sample we identified 13% (9/67) as potential clozapine PMs needing from 91 to 119 mg/day to get a therapeutic concentration of 350 ng/ml (Supplemental Table S6). It was reassuring that 2 of 3 (67%) excluded due to intake of inhibitors were phenotypic clozapine PMs (Supplemental Table S5, footnote a).

In the Vellore sample, there were four possible phenotypic clozapine PMs (three due to obesity and one due to valproate) (Supplemental Table S5), along with 2% who were potentially clozapine PMs (2/101) (Supplemental Table S6).

Prevalence of clozapine UMs in 4 new Asian samples

After stratification by sex and smoking status, there were no clozapine UMs in the Taipei sample. In the other samples we found 1.6% (3/191) in Beijing Sample 2, 1.5% (1/67) in the Seoul sample, and 3% (3/101) in the Vellore sample (Supplemental Table S6). Lack of adherence may be the most reasonable explanation for most of those who had extremely low total clozapine C/D ratios, around 0.30, indicating the need of doses around 1167 mg/day to reach a concentration of at least 350 ng/ml. We have seen these very low total clozapine C/D ratios only in a US UM with extreme sensitivity to induction.[21] In a Vellore UM, a clozapine C/D ratio of 0.34 in a female non-smoker was compatible with extreme induction after drinking 10 cups of coffee.

Discussion

In our four Asian samples, the prevalence of potential PMs ranged from 2-13%, but inflammation was not excluded in all 4 samples and non-psychiatric inhibitors were not excluded

in one (Beijing 2). This prevalence is similar to Beijing Sample 1 in which, after excluding inflammation and inhibitors, we had found a phenotypic PM prevalence of 4%.[11]

Future studies of clozapine PMs

Powerful clozapine inhibitors such as fluvoxamine, oral contraceptives or inflammation can make a patient a phenotypic clozapine PM, but this study has, for the first time, described five possible PMs associated with extreme obesity.[19] Future studies incorporating DNA sequencing to identify currently unknown mutations associated with PM status in Asian patients may establish the true prevalence of clozapine PMs. Until then, clinicians should assume that around 10% of Asian patients, who are not taking inhibitors or suffering infections, may need very low clozapine doses (between 50-150 mg/day) to reach clozapine therapeutic concentrations.

In 152 Italian Caucasian outpatients, we found a prevalence of 3.3% for phenotypic clozapine PMs, who needed 59-100 mg/day to get at least 350 ng/ml.[11] The Italian sample was limited by single TDM measures in most patients and possible contamination by infection, non-psychiatric CYP1A2 inhibitors or obesity. Future studies with repeated measures and careful control of confounders including inhibitors, inflammation and obesity should provide better estimations of the prevalence of phenotypic clozapine PMs in Caucasians and identify the underlying allele, CYP1A2*7 or other unknown alleles associated with being a clozapine PM. Studies on clozapine PM prevalence and underlying alleles are needed in other races.

Future studies of clozapine UMs

The prevalence of UMs was 0% of 126 in Beijing Sample 1 after excluding one patient on carbamazepine. Among the 4 Asian samples in this study, we found 0% (0/85) in the Taipei sample, 1.5% (1/67) in the Seoul sample; 1.6% (3/191) in Beijing Sample 2, and 3% (3/101) in

the Vellore sample. Thus, by adding the four samples we found 7 Asian phenotypical UMs. From these seven patients only one had a good explanation for phenotypic UM status. This Vellore patient was consuming a large amount of coffee and needed 1029 mg/day of clozapine to reach a TDM of 350 ng/ml had. The other 6 patients had extremely low total clozapine C/D ratios, each based on a single measure, so we cannot rule out lack of adherence as an explanation for those low clozapine C/D ratios.

Studying clozapine UMs is much more complicated than studying clozapine PMs. In inpatient studies with careful supervision of compliance,[27] multiple measures are needed to establish that a patient is really a clozapine UM. Phenotypic clozapine UMs may be explained by well-established potent inducers such as carbamazepine, phenytoin or rifampin. Moreover, according to single cases, very low total clozapine C/D ratios in the UM range may possibly be explained by unusual potent induction secondary to the combination of valproate and smoking[20] or consuming huge quantities of coffee in India. In South Asian populations,[26] high coffee intake has been associated with induction of CYP1A2 expression, possibly by the way the coffee beans are toasted. These compounds found in coffee bind to the aryl hydrocarbon receptor (AhR)[15]and have the same inductive properties, such as the polycyclic aromatic hydrocarbons found in tobacco smoking or barbecued food.

The prevalence of clozapine UMs in different races is currently unknown and in our review[11] of all 13 published cases we found that in most patients lack of compliance and/or potent inducers were not ruled out by the authors of the respective articles.

Limitations

This study used already published Asian studies with no genetic testing and clozapine TDM samples which did not follow the same standardized methods; on the other hand,

Supplementary Table S3 suggests that the mean C/D ratios after sex and smoking stratification were very similar. Lack of adherence may be the greater study confounder since only one TDM sample was measured in all 4 studies and 3 of 4 studies include outpatients. Inflammation as a possible confounder of phenotypic PM status was not studied in any of the 4 studies. Non-psychiatric inhibitors may contaminate one of the studies (Beijing 2).

Conclusion

In our four Asian extension samples, the prevalence of potential PMs ranged from 2-13%, but inflammation was not excluded, which is similar to the published 4% in our Beijing Sample 1 after excluding inflammation (and inhibitors).[11] Clinicians need to be aware that around 10% of Asians may be clozapine PMs and may only need 50-150 mg/day to reach therapeutic concentrations. Future studies should combine gene sequencing for new alleles with repeated concentrations and careful control of confounders including inhibitors, inflammation and obesity, which should provide better estimations of the prevalence of phenotypic clozapine PMs across races. Researchers need to explore which new alleles besides CYP1A2*7 may explain clozapine PM status in the absence of confounders. Studying clozapine UMs is much more complicated than performing clozapine PM studies. Inpatient studies with careful supervision of compliance and multiple measures are needed to establish that a patient is really a clozapine UM; potent inducers need to be ruled out. Until these studies are completed, the prevalence of clozapine UMs across races is unknown.

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Can-Jun Ruan, Ph.D.; Chuan-Yue Wang, M.D., Ph.D.; Yi-Lang Tang, M.D., Ph.D.; Shih-Ku Lin, M.D.; Seung-Tae Lee, M.D., Ph.D.; Kyung Sue Hong, M.D., Ph.D.; Anto P. Rajkumar, M.D.; Kuruthukulangara S. Jacob, M.D., Ph.D.; Jose de Leon, M.D.

This Supplemental Material includes 6 Supplemental Tables.

Supplemental Table S1. Definition of cut scores of clozapine C/D ratios (ng/ml per mg/day) for Asian clozapine PMs and UMs based on Beijing Sample 1.[11]

	PMs		UMs	
	Total	Clozapine	Total	Clozapine
♂ smokers	>3.66	>2.53	<0.30	<0.15
♀ smokers	>3.35	>2.65	<0.67	<0.35
♂ non-smokers	>4.57	>3.27	<0.49	<0.15
♀ non-smokers	>4.97	>3.60	<0.97	<0.63

C/D indicates concentration/dose; PM, poor metabolizer; UM, ultrarapid metabolizer.

Supplemental Table S2. Mean clozapine C/D ratios and description of sex and smoking status in 4 samples compared with Beijing 1 Sample

				C/D ratio								Dose to reach
	N	Age	Dose	Clozapine	Total	% Smokers		Non-smokers		Setting	N[a]	350 ng/ml[b]
		(year)	(mg/day)			♂	♀	♂	♀			(mg/day)
Beijing 1	126	43.6	226	1.84±0.78	2.63±1.04	17	4	28	51	inpatients	9.3	190
Beijing 2	191[c]	43.7`	297	1.66±1.28	2.35±1.65	26	1	34	39	inpatients	1	211
Taipei	85[d]	37.2`	281	1.83±1.18	2.68±1.64	26	4	34	36	outpatients	1	191
Seoul	67[e]	33.1`	331	1.87±0.97	2.87±1.39	22	2	39	37	outpatients	1	187
Vellore	101	35.4`	340	1.71±1.12		19	0	53	28	out/inpatients[f]	1	204

[a]Number of samples per patient. In Beijing Sample 1, multiple samples were available for each patient (mean of 9.3). In each patient, the samples were averaged to provide a more precise estimation of clozapine C/D ratios. Other studies used a single concentration per patient.

[b]Mean clozapine daily dose needed to reach a concentration of 350 ng/ml was calculated by dividing 350 by mean clozapine C/D ratio.

[c]Patients with hepatic and/or renal impairment were excluded. Patients using herbal medicines, antidepressants, mood stabilizers or anticonvulsants were excluded, but those using benzodiazepines and anticholinergics were included.

[d]Excluded patients include 9 in which sex was not specified, 1 who was on carbamazepine and 7 who were on fluvoxamine.

[e]Excluded patients include 1 on fluvoxamine and 2 on clorimipramine.

[f]There were a few inpatients.

C/D indicates concentration-to-dose measured in ng/ml per mg/day.

Supplemental Table S3. Mean clozapine C/D ratios after stratification by sex and smoking status compared with Beijing 1 sample

					C/D ratio (ng/ml per mg/day)		Dose to reach[a]
Group	Sample	N	Age (year)	Dose (mg/day)	Clozapine	Total	>350 ng/ml (mg/day)
♂ smokers	Beijing 1	22	46.6	271	1.34±0.59	1.98±0.84	261
	Beijing 2	49	40.6	341	1.31±0.95	1.90±1.22	267
	Taipei	22	36.1	286	1.19±0.54	1.82±0.84	294
	Seoul	15	37.3	378	1.35±0.71	2.05±1.01	259
	Vellore	19	39.0	401	1.29±1.07		271
♀ smokers	Beijing 1	5	54.6	301	1.50±0.58	1.90±1.22	NC[b]
	Beijing 2	2	39.0	313	1.11±0.46	1.50±0.46	NC[b]
	Taipei	3	36.3	325	1.24±0.48	2.03±0.80	NC[b]
	Seoul	1	38	450	0.88	1.59	NC[b]
♂ non-smokers	Beijing 1	35	37.2	230	1.71±0.78	2.49±1.04	205
	Beijing 2	65	42.8	262	1.50±0.90	2.12±1.12	233
	Taipei	29	36.0	300	1.80±1.07	2.65±1.42	194
	Seoul	26	31.0	347	1.70±0.84	2.58±1.02	206
	Vellore	54	33.8	329	1.78±1.19		197
♀ non-smokers	Beijing 1	64	45.1	202	2.11±0.74	2.97±1.00	166
	Beijing 2	75	46.5	297	2.03±1.64	2.87±2.12	172
	Taipei	31	39.1	254	2.38±1.41	3.38±2.00	147
	Seoul	25	32.4	282	2.41±1.02	3.72±1.52	145
	Vellore	28	36.2	323	1.85±1.16		189

[a]Mean dose needed to reach a concentration of 350 ng/ml was calculated by dividing 350 by mean clozapine C/D ratio.

[b]The samples are too small in size to provide a mean dose estimation.

C/D indicates concentration-to-dose measured in ng/ml per mg/day; NC, not calculated.

Supplemental Table S4. C/D ratios in phenotypic clozapine PMs with known confounders

	C/D ratio		Dose (mg/day)[a]	
Age/sex/smoking	Total	Clozapine	for 350 ng/ml	Possible known confounders
Beijing Sample 2: 2 patients with very high BMI, which may explain low clozapine clearance				
43yo ♀ non-smoker	5.19	6.37	> 67	BMI=35.5
46yo ♀ non-smoker	4.43	5.99	> 79	BMI=35.7
Taipei: no phenotypical PMs in 70 study patients[b]				
Seoul: no phenotypical PMs in 67 study patients[c]				
Vellore: 4 patients with high BMI or valproate, which may explain low clozapine clearance				
48yo ♀ non-smoker		5.15	>68	BMI=31.4
27yo ♂ non-smoker		3.70	>95	BMI=28.7
34yo ♂ smoker		3.32	>105	Valproate
34yo ♂ smoker		2.90	>121	BMI=29.3

[a]Mean clozapine daily dose needed to reach a concentration of 350 ng/ml was calculated by dividing 350 by mean clozapine C/D ratio.

[b]Nine patients on fluvoxamine were not included among the 70 study patients. It was reassuring that 6 of them (67%) were clozapine PMs, according to their sex and smoking status group; they had total clozapine C/D ratios ranging from 7.48 to 5.11 ng/ml per mg/day.

[c]Three patients were not included among the 67 study patients due to use of fluvoxamine or clomipramine. It was reassuring that 2 of them (67%) were clozapine PMs according to their sex and smoking status group. A male non-smoker on fluvoxamine had a total clozapine C/D ratio of 5.76 ng/ml per mg/day. Simultaneously, a male smoker had a very high total clozapine C/D ratio of 6.47 ng/ml per mg/day, possibly explained by three confounders (co-medication with clomipramine, and propranolol,

and a possible infection since his WBC was the highest in the Seoul sample with a value of 14.8 x 10^9 cell/L).

BMI indicates body mass index; C/D, concentration/dose measured in ng/ml per mg/day; PM, poor metabolizer.

Supplemental Table S5. C/D ratios in phenotypic clozapine PMs with no known confounders

	C/D ratios		Dose (mg/day) [a]	
Age/sex/smoking	Total	Clozapine	for 350 ng/ml	Possible Confounders
Beijing Sample 2: 14 possible PMs (7.3% of 191)				
63yo ♀ non-smoker	10.31	13.70	> 34	INF, non-psychiatric inhibitors[b]
51yo ♀ non-smoker	5.69	7.15	> 62	INF, non-psychiatric inhibitors[b]
63yo ♀ non-smoker	5.49	6.71	> 64	INF, non-psychiatric inhibitors[b]
42yo ♀ non-smoker	5.23	7.28	> 67	INF, non-psychiatric inhibitors[b]
48yo ♂ smoker	5.10	6.33	> 69	INF, non-psychiatric inhibitors[b]
34yo ♂ smoker	4.43	6.12	> 79	INF, non-psychiatric inhibitors[b]
18yo ♀ non-smoker	4.12	5.96	> 85	INF, non-psychiatric inhibitors[b]
40yo ♀ non-smoker	4.12	5.04	> 85	INF, non-psychiatric inhibitors[b]
72yo ♀ non-smoker	3.96	5.72	> 88	INF, non-psychiatric inhibitors[b]
61yo ♀ non-smoker	3.70	5.12	> 95	INF, non-psychiatric inhibitors[b]
44yo ♂ non-smoker	3.67	4.67	> 95	INF, non-psychiatric inhibitors[b]
74yo ♀ non-smoker	3.40	5.15	> 103	INF, non-psychiatric inhibitors[b]
53yo ♂ non-smoker	3.03	4.74	> 116	INF, non-psychiatric inhibitors[b]
38yo ♂ smoker	2.74	4.22	> 128	INF, non-psychiatric inhibitors[b]
Taipei: 8 possible PMs (11% of 70)[c]				
39yo ♀ non-smoker	8.49	11.9	> 41	INF
22yo ♂ non-smoker	4.92	6.66	> 71	INF
27yo ♀ non-smoker	4.33	6.41	> 81	INF
37yo ♂ non-smoker	3.66	5.50	> 96	INF

43yo ♂ non-smoker	3.66	4.83	> 96	INF
34yo ♀ non-smoker	3.63	5.81	> 97	INF
44yo ♂ non-smoker	3.48	4.78	> 101	INF
46yo ♂ smoker	2.18	3.93	> 161	INF
Seoul: 9 possible PMs (13% of 67)[c]				
23yo ♀ non-smoker	3.84	6.52	> 91	INF
24yo ♂ non-smoker	3.77	4.71	> 93	INF
24yo ♀ non-smoker	3.71	6.00	> 94	INF
36yo ♀ non-smoker	3.72	5.73	> 94	INF
45yo ♀ non-smoker	3.60	5.22	> 97	INF
37yo ♀ non-smoker	3.48	4.98	> 101	INF
45yo ♀ non-smoker	3.38	5.26	> 104	INF
32yo ♀ non-smoker	3.36	5.17	> 104	INF
50yo ♂ smoker	2.95	4.96	> 119	INF
Vellore: 2 possible PMs (2% of 101)				
35yo ♂ non-smoker		8.29	>42	INF
35yo ♀ non-smoker		5.09	>69	INF

[a]Mean clozapine daily dose needed to reach a concentration of 350 ng/ml was calculated by dividing 350 by the mean clozapine C/D ratio.

[b]Oral contraceptives were not used at that time by fertile females at that hospital when the study was completed; other non-psychiatric inhibitors are very rarely prescribed in this hospital and are not likely to explain the low clearance.

[c]Although we had no heights for calculating BMI, the weights of these PM patients were not compatible with extreme obesity.

BMI indicates body mass index; C/D, concentration/dose measured in ng/ml per mg/day; INF, inflammation; PM, poor metabolizer.

Supplemental Table S6. C/D ratios of phenotypic clozapine UMs

	C/D ratios		Dose (mg/day)	
Age/sex/smoking	Total	Clozapine	for 350 ng/ml[a]	Possible Confounders
Beijing Sample 2 (3 UMs: 1.6% of 191)				
47yo ♀ non-smoker	0.47	0.26	>1346	Lack of adherence (inpatient)
52yo ♂ non-smoker	0.47	0.35	>1000	Lack of adherence (inpatient)
43yo ♀ non-smoker	0.62	0.46	>761	Lack of adherence (inpatient)
Seoul (1 UM: 1.5% of 67)				
26yo ♀ non-smoker	0.97	0.52	> 671	Lack of adherence (outpatient)
Vellore (3 UMs: 3% of 101)				
31yo ♀ non-smoker		0.29	> 1211	Lack of adherence (outpatient)
31yo ♀ non-smoker		0.34	> 1016	10 cups of coffee may contribute
40 yo ♀ non-smoker		0.54	> 653	Lack of adherence (outpatient)

[a]Mean clozapine daily dose needed to reach a concentration of 350 ng/ml was calculated by dividing 350 by mean clozapine C/D ratio.

C/D indicates concentration/dose measured in ng/ml per mg/day; UM, ultrarapid metabolizer.