

Use of Clozapine for the Treatment of Schizophrenia: Findings of the 2006 Research on the China Psychotropic Prescription Studies

Tian-Mei Si¹, Yun-shu Zhang², Liang Shu¹, Ke-Qing Li², Xie-He Liu³, Qi-Yi Mei⁴, Gao-Hua Wang⁵, Pei-Shen Bai⁷, Li-Ping Ji⁶, Xian-Sheng Cheng⁸, Cui Ma⁹, Jian-Guo Shi¹⁰, Hong-Yan Zhang¹, Hong Ma¹, Xin Yu¹

¹Peking University Institute of Mental Health, Beijing, ²Hebei Mental Health Center, Baoding, ³Mental Health Center of Huaxi Hospital, Sichuan University, Chengdu, ⁴Guangji Hospital, Suzhou, ⁵Department of Mental Health, People's Hospital of Wuhan, Wuchang, ⁶Jilin Neuro-Psychiatric Hospital, Siping, ⁷The First Hospital of Shanxi Medical University, Taiyuan, ⁸Jiangxi Mental Health Hospital, Nanchang, ⁹Guanzhou Mental Health Hospital, Guangzhou, ¹⁰Xi'an Mental Health Center, Xi'an, China

Objective: Clozapine is one of the most commonly used antipsychotic drugs in China. To date, few studies have investigated the patterns the prescription of clozapine nationwide. The present study examined these patterns in China in 2006 and identified the demographic and clinical characteristics associated with the use of clozapine.

Methods: Using a standardized protocol and data collection procedure, we surveyed 5,898 patients with schizophrenia in 10 provinces with differing levels of economic development.

Results: Overall, clozapine had been prescribed for 31.9% (n=1,883) of the patients; however we found considerable variation among the 10 provinces. The frequency of clozapine use was highest in Sichuan (39.3%) and lowest in Beijing (17.3%). The mean daily dose of clozapine was 210.36 ± 128.72 mg/day, and 25.1% of the patients were treated with clozapine in combination with other antipsychotics. Compared with the group not receiving clozapine, clozapine-user had been treated for longer durations and had experienced a greater number of relapses and hospitalizations. Furthermore, those in the clozapine-user had lower family incomes, were less able to seek psychiatric services, and more likely to be male and have a positive family history of schizophrenia. A multiple logistic regression analysis revealed that age, sex, professional help-seeking behaviors, duration of illness, economic status, educational level, and clinical manifestations were associated with the use of clozapine.

Conclusion: Clozapine use is common in China. However, use of the antipsychotic varies among provinces, and demographic and clinical factors play important roles in the prescription of clozapine.

KEY WORDS: Schizophrenia; Clozapine; Prescription; Sampling studies.

INTRODUCTION

Clozapine, the first atypical antipsychotic, was widely used following its introduction because it induced relatively few extrapyramidal effects, and it showed therapeutic benefit for patients who had failed to respond to other agents.¹⁾ However, several cases of clozapine-induced agranulocytosis reported in Europe led to withdrawal of the drug in European countries and delayed further development of the antipsychotic in the United States.²⁾ Because of the unique efficacy of clozapine for

the treatment of refractory schizophrenia, the U.S. Food and Drug Administration approved the limited use of this medicine to treat refractory schizophrenia in 1990 under a strict monitoring and dispensing system instituted by the Clozapine National Registry.³⁾ At present, most guidelines recommend that clozapine be used as a second-line medication reserved for treatment-resistant schizophrenia.^{4,5)} To some extent, clozapine has served as a prototype and stimulus for the development of new antipsychotics.

Clozapine was introduced in China in the 1970s and, unlike most countries, China used the antipsychotic as the first-line treatment for schizophrenia and other psychotic disorders for several years,⁶⁾ and it remained the first-choice treatment for patients with schizophrenia throughout the 1990s. The primary reason Chinese physicians embraced clozapine for the treatment of schizophrenia was the reduced risk of tardive dyskinesia,⁷⁾ the drug's efficacy and low cost further contributed to the popularity of cloza-

Received: November 14, 2011 / **Revised:** February 24, 2012

Accepted: May 11, 2012

Address for correspondence: Tian-Mei Si, MD

Department of Psychopharmacology, Institute of Mental Health, Peking University, No.51 Hua Yuan Bei Road, Haidian District, Beijing 100191, China

Tel: +86-10-82801948, Fax: +86-10-62027314

E-mail: si.tian-mei@163.com

pine among clinicians and patients.^{8,9)} To date, few studies have investigated the patterns characterizing the prescription of clozapine for the treatment of schizophrenia in China. The objectives of the present study were to describe these patterns and to compare the sociodemographic and clinical characteristics of patients with schizophrenia taking and not taking clozapine.

METHODS

Setting, Study Design, and Subjects

The data for the present study were taken from a nationwide investigation of antipsychotic medication prescriptions. China's Gross Domestic Product in 2000 indicated that the country's provinces could be divided into five economic levels. The present study included 10 provinces with at least one at each economic level. One city was chosen from each selected province: level I included Beijing, Suzhou, and Guangzhou; level II included Baoding; level III included Siping and Wuhan; level IV included Taiyuan; and level V included Xi'an, Nanchang, and Chengdu. Mental health hospitals in each selected city were divided into three categories according to their academic level.

The present cross-sectional study was conducted between May 22 and 28, 2006 using a standardized protocol and data collection procedure. The sample population consisted of outpatients and inpatients diagnosed with schizophrenia according to the criteria of the International Classification of Diseases and Related Health Problems 10th revision who were interviewed or treated in the selected hospitals. The study protocol was approved by the Human Research and Ethics Committee of the Institute of Mental Health, Peking University. Written consent was obtained from all subjects.

A uniform questionnaire designed to collect data on demographic characteristics, clinical factors, physical condition, duration of illness, and prescribed antipsychotic and dose was administered to all patients. One section of the questionnaire documented symptoms during the previous month and medication-induced adverse effects. The Clinical Global Impression Scale-severity was used to assess the severity of the illness.

Statistical Analysis

SPSS version 13 (SPSS Inc., Chicago, IL, USA) was used to conduct the statistical tests. Frequency tables were constructed to measure categorical data and descriptive

analyses were performed for all data. Determination of the frequency of clozapine prescription and the comparison of sociodemographic and clinical characteristics between clozapine user and non-user groups were performed using independent sample *t*-tests, the chi-square test, and Fisher's exact test, as appropriate.

A multiple stepwise logistic regression analysis was performed to adjust for relevant covariates and to determine the predictors of clozapine use. A Kolmogorov-Smirnov one-sample test was used to test the normality of the distribution of the continuous variables. *p*-values < 0.05 (two-tailed) were deemed to be statistically significant.

RESULTS

A total of 5,898 patients with schizophrenia from 10 provinces were recruited to participate in the present study. Overall, 31.9% of the patients (*n*=1,883) were prescribed clozapine; however, considerable variation existed among the 10 provinces. Table 1 shows the sociodemographic and clinical characteristics of clozapine users according to study site. Clozapine doses differed significantly among the 10 sites (mean, 210.36±128.72 mg/day; range, 155.99±103.42-240.83±154.24 mg/day) with the frequency of use highest in Sichuan province (39.3%) and lowest in Beijing (17.3%). Moreover, the prescribing pattern of clozapine differed among the 10 sites, with 25.1% of the patients receiving clozapine in combination with other antipsychotics.

Table 2 shows the sociodemographic and clinical characteristics of clozapine users (*n*=1,883) and non-users (*n*=4,015). Compared with the non-clozapine group, the clozapine-treated patients had been under treatment for a longer period of time and had had more experiences of relapse and hospitalization. Clozapine-treated patients had lower family incomes, were less able to seek psychiatric services, and were more likely to be male and have a positive family history of schizophrenia than were patients not treated with clozapine. The clinical characteristics of clozapine users and non-users differed significantly. Compared with the non-users, clozapine users were more likely to show speech and behavioral disturbances, aggressive behavior, and have negative symptoms and functional impairment.

Table 3 shows the results of the multiple logistic regression analysis revealing the independent factors that were significantly associated with clozapine use. These factors

Table 1. Socio-demographic and clinical characteristics in the clozapine-users

	Beijing n=456	Hebei n=981	Sichuan n=646	Jiangsu n=384	Hubei n=408	Jilin n=338	Shanxi n=534	Shanxi n=566	Jiangxi n=506	Guangdong n=1,079	p value
Clozapine-treated, n (%)	79 (17.3)	347 (35.4)	254 (39.3)	117 (30.5)	124 (30.4)	116 (34.3)	192 (36.0)	175 (30.9)	183 (36.2)	296 (27.4)	<0.001
Age (yr, mean±SD)	46.33±12.56	34.76±11.90	39.70±13.70	43.03±12.79	29.30±10.29	34.53±9.97	33.49±9.92	32.39±10.52	34.11±11.62	38.41±11.64	<0.001
Gender											0.059
Male	39	156	92	72	35	53	84	61	89	130	
Female	36	130	79	31	41	42	71	54	56	89	
Missing	0	3	0	0	2	0	2	0	4	3	
Family history											0.004
Positive	16	77	71	41	31	25	59	37	46	48	
Negative	56	255	181	76	88	88	130	134	135	236	
Missing	7	15	2	0	5	3	3	4	2	12	
Admission times (median)	0	0	1	0	0	1	0	0	0	1	<0.001
Episodes (median)	1	1	1	1	1	1	1	1	1	1	<0.001
Family income (RMB/month, median)	3,000	1,000	1,550	1,800	1,200	900	1,000	1,000	1,200	3,000	<0.001
Settings											<0.001
Outpatient	25	74	67	44	29	55	68	47	67	67	
Inpatient	50	215	104	59	49	40	89	68	82	155	
Polyparmacy, n (%)	4 (5.1)	113 (32.6)	85 (33.5)	25 (21.4)	31 (25.0)	20 (17.2)	40 (20.8)	53 (30.3)	33 (18.0)	68 (23.0)	<0.001
Daily dose (mean±SD)	236.2±128.2	213.0±116.9	195.4±129.6	203.2±120.1	156.0±103.4	233.9±138.6	240.8±154.2	183.0±137.8	224.9±119.6	217.2±121.5	<0.001

n=1,883. RMB, renminbi; SD, standard deviation.

(age, sex, duration of illness, economic status, educational level, and clinical manifestations) played an important role in determining whether clozapine was prescribed.

DISCUSSION

Clozapine was widely used in China after its introduction in 1976 and, by the end of the 1980s, it had become the first-line treatment for schizophrenia and other psychotic disorders. After 2000, despite the availability of other second-generation antipsychotic drugs, clozapine remained widely prescribed in China, primarily because the drug was associated with fewer drug-induced extrapyramidal effects, particularly tardive dyskinesia.⁷⁾ Moreover, ample medical evidence has demonstrated that clozapine is more effective than any other antipsychotic for treating schizophrenia and that it has a clear superiority over the other antipsychotic drugs for the treatment of refractory schizophrenia.¹⁰⁻¹²⁾ Furthermore, the low cost of treatment contributed to its popularity in clinical practice. We found that the use of clozapine differed among the 10 provinces studied. Higher economic levels were associated with less clozapine use, and patients with higher clozapine use had a lower family income. The multiple logistic analysis revealed that clozapine users were more likely to suffer from chronic and refractory schizophrenia and more likely to have behavioral disturbances or functional impairment than were patients who were not treated with clozapine. These clinical characteristics appeared to be indicators for clozapine treatment.

Clozapine is associated with several severe adverse effects including agranulocytosis, bowel infarction, seizures, myocarditis, and diabetes,^{13,14)} and the less serious adverse effects of sialorrhea and weight gain.¹⁵⁾ Most guidelines recommend that clozapine be used only to treat refractory schizophrenia.^{4,16)} The frequency of clozapine prescriptions decreased in China between 2002 (39%) and 2006 (31.9%),¹⁷⁾ but remained higher than that in the United States and Europe.^{18,19)} This difference between China and United States and Europe may be explained by the availability and low cost of the medication and the blood-monitoring requirements established by local regulations.²⁰⁾

Our results revealed that the average dose of clozapine was 210.36±128.72 mg/day for Chinese patients, which is consistent with the findings of Chen and Si¹⁷⁾ but lower than that reported in the United States and Europe.^{21,22)} This discrepancy may be explained by racial differences in pharmacokinetic and pharmacodynamic variables.²³⁾

Table 2. Comparison of the clozapine and non-clozapine groups with regard to socio-demographic and clinical characteristics in the whole sample

	Clozapine-users (n=1,883)	Non-clozapine users (n=4,015)	t/ χ^2	p value
Age (year)	36.21±12.32	35.82±14.31	-1.024	0.306
Gender			24.429	<0.001
Male	1,059 (56.2)	1,982 (49.4)		
Female	807 (42.9)	1,996 (49.7)		
Missing	17 (0.9)	37 (0.9)		
Family history			9.531	0.002
Positive	451 (24.0)	819 (20.4)		
Negative	1,379 (73.2)	3,079 (76.7)		
Missing	53 (2.8)	117 (2.9)		
Settings			96.290	<0.001
Outpatient	692 (36.7)	2,024 (50.4)		
Inpatient	1,191 (63.3)	1,991 (49.6)		
Duration of illness (month)	84	36	120.555	<0.001
Family income (RMB/month)	1,300	2,000	26.237	<0.001
Relapse episodes	3	2	61.173	<0.001
Speech and behavioral disturbance	983 (52.2)	1,864 (46.4)	17.138	0.000
Negative symptoms	894 (47.5)	1,566 (39.0)	37.857	0.000
Retardation or agitation	20 (1.1)	77 (1.9)	5.802	0.016
Functioning impairment	1,409 (74.8)	2,732 (68.0)	28.194	0.000
Aggressive behaviors	439 (23.3)	698 (17.4)	28.957	0.000

n=5,898. Values are presented as mean±standard deviation, number (%), or median. RMB, renminbi.

Alternatively, as 25.1% of our patients were treated using a combination of clozapine and other medications, the dose of clozapine was relatively low. Finally, the fact that clozapine is used only to treat refractory schizophrenia in the United States and Europe, whereas some regions in China use clozapine as a first-line therapy may underlie differences in drug dose. Furthermore, we found regional differences in the use of clozapine either alone or in combination with other drugs. Clozapine was prescribed least frequently in Beijing province (17.3% alone and 5.1% in combination with other drugs) and most frequently in Sichuan province (39.3% alone and 33.5% in combination with other drugs). The lowest dose of clozapine was found in Hubei (155.99±103.42 mg/day) and the highest in Shanxi (240.83±154.24 mg/day). These differences may be related to local healthcare systems, patients' clinical profiles and family economic status, and clinicians' prescribing habits.^{21,24)}

Several studies have reported that male patients are more likely than female patients to experience refractory schizophrenia and have chronic onset. Moreover, the duration of hospitalization was longer in male patients, and their main clinical features were prominent positive and negative symptoms accompanied by comprehensive social dysfunction.^{21,25,26)} The survey results indicated that Chinese physicians in 2006 were more likely to use cloza-

pine as a second-line treatment for refractory schizophrenia than as a first-line treatment. Two conclusions can be drawn from the analysis of factors influencing clozapine prescribing patterns. First, physicians in regions outside of Beijing were the most likely to prescribe clozapine. Second, clozapine was more likely to be prescribed for hospitalized patients with a less education, less family income, longer hospitalizations, verbal and behavioral disorders, negative symptoms, and frequent episodes of schizophrenia.

The present study has several limitations. As a cross-sectional survey with no long-term follow up of patients, it could not systematically evaluate the efficacy and adverse side effects of clozapine. Moreover, treatment decisions depend on patient factors and physician prescribing practices. However, our study examined only patient factors, and the factors affecting physicians' prescribing practices were not explored.

In summary, the survey results show that clozapine is commonly prescribed in China and that economic and clinical factors, along with the characteristics of treatment settings, contribute to clozapine-prescription patterns. The risk of clozapine-induced granulocytosis and metabolic syndrome require that regular blood and metabolic monitoring be strictly performed in clinical practice.

Table 3. Factors associated with use of clozapine (multiple logistic regression analysis)

	B	SE	Wald	p value	OR	OR 95%CI	
						Lower	Upper
Age	-0.020	0.006	11.058	0.001	0.981	0.969	0.992
Gender	-0.153	0.066	5.305	0.021	0.858	0.753	0.977
Settings	0.580	0.071	66.227	0.000	1.786	1.553	2.053
Region*			69.026	0.000			
Region (1)	0.847	0.174	23.754	0.000	2.332	1.659	3.279
Region (2)	1.159	0.175	43.981	0.000	3.186	2.262	4.487
Region (3)	0.831	0.197	17.745	0.000	2.296	1.560	3.380
Region (4)	0.881	0.198	19.834	0.000	2.414	1.638	3.557
Region (5)	0.874	0.212	16.996	0.000	2.398	1.582	3.634
Region (6)	1.032	0.184	31.418	0.000	2.806	1.956	4.025
Region (7)	0.687	0.185	13.747	0.000	1.988	1.383	2.859
Region (8)	0.915	0.189	23.388	0.000	2.497	1.723	3.618
Region (9)	0.450	0.173	6.762	0.009	1.568	1.117	2.200
Duration of illness	0.005	0.001	36.308	0.000	1.005	1.004	1.007
Family income	0.000	0.000	5.138	0.023	1.000	1.000	1.057
Educational level [†]			21.709	0.001			
Educational level (1)	0.021	0.221	0.009	0.925	1.021	0.662	1.575
Educational level (2)	0.325	0.211	2.371	0.124	1.384	0.915	2.094
Educational level (3)	0.150	0.219	0.468	0.494	1.161	0.756	1.783
Educational level (4)	0.022	0.249	0.008	0.931	1.022	0.627	1.665
Educational level (5)	-0.196	0.252	0.605	0.437	0.822	0.502	1.346
Educational level (6)	-0.077	0.266	0.084	0.772	0.926	0.550	1.559
Occupation [‡]			45.395	0.000			
Occupation (1)	-0.272	0.146	3.492	0.062	0.762	0.573	1.013
Occupation (2)	-0.822	0.144	32.516	0.000	0.439	0.331	0.583
Occupation (3)	0.026	0.095	0.076	0.783	1.027	0.851	1.238
Occupation (4)	-0.030	0.101	0.090	0.764	0.970	0.796	1.182
Occupation (5)	0.102	0.269	0.144	0.704	1.107	0.654	1.874
Occupation (6)	-0.490	0.185	6.964	0.008	0.613	0.426	0.882
Occupation (7)	-0.079	0.176	0.203	0.652	0.924	0.654	1.304
Speech and behavioral disturbances	0.209	0.072	8.410	0.004	1.232	1.070	1.418
Negative symptoms	0.269	0.069	14.974	0.000	1.309	1.142	1.499
Aggressive behaviors	0.269	0.069	14.974	0.000	1.309	1.142	1.499

n=5,898.

B, regression coefficient; SE, standard error; OR, odds ratio; CI, confidence interval.

*Region (1)-(9) represents Hebei, Sichuan, Jiangsu, Hubei, Jilin, Shanxi, Shaanxi, Jiangxi and Guangdong, and Beijing is the reference in the regression model.

†Educational level (1)-(6) represents primary school or below, junior middle school, high school/vocational high school, secondary technical school, junior college and university or above, and illiteracy is the reference in the regression model.

‡Occupation (1)-(7) represents retired, student, farmer, worker, civil servant, company/enterprise employees, institutions/Authority units personnel, and unemployed is the reference in the regression model.

■ Acknowledgments

This study was supported in part by grants from the Capital Development Foundation (No. 2009-2026). The authors are grateful to the all clinicians involved in the data collection. The authors also thank clinicians who helped to organize the study in each study site.

REFERENCES

- Nielsen J, Dahm M, Lublin H, Taylor D. *Psychiatrists' attitude towards and knowledge of clozapine treatment. J Psychopharmacol* 2010;24:965-971.
- Kane J, Honigfeld G, Singer J, Meltzer H. *Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. Arch Gen Psychiatry* 1988;45:789-796.
- Kane JM, Correll CU. *Pharmacologic treatment of schizophrenia. Dialogues Clin Neurosci* 2010;12:345-357.
- Shu L. *Chinese Guideline for Schizophrenia [M]. Beijing: Peking University Medical College press:2007. p.43-46.*
- Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, et al; American Psychiatric Association; Steering Committee on Practice Guidelines. *Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry* 2004;161(2 Suppl):1-56.
- Wu TC, Tang GR. *Clinical use of antipsychotics and follow-up study. Chin J Neuropsychiat* 1995;28:217-219.
- Han QK, Ruan J. *Effects of clozapine to treat the Tardive Dyskinesia. J Clin Psychol Med* 2003;13:30-31.
- Si TM, Shu L, Yu X, Ma C, Wang GH, Bai PS, et al. *Antipsychotic drug patterns of schizophrenia in China: a cross sectional study. Chinese J Psychiatry* 2004;37:152-155.
- Si TM, Shu L, Yu X, Ma C, Wang GH, Bai PS, et al.

- The second cross-sectional study on antipsychotic drug patterns of schizophrenia in China. Chinese J Psychiatry* 2010;43:31-36.
10. Leucht S, Heres S, Kissling W, Davis JM. Evidence-based pharmacotherapy of schizophrenia. *Int J Neuropsychopharmacol* 2011;14:269-284.
 11. Tandon R, Belmaker RH, Gattaz WF, Lopez-Ibor JJ Jr, Okasha A, Singh B, et al; Section of Pharmacopsychiatry, World Psychiatric Association. World Psychiatric Association Pharmacopsychiatry Section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. *Schizophr Res* 2008;100:20-38.
 12. Iqbal MM, Rahman A, Husain Z, Mahmud SZ, Ryan WG, Feldman JM. Clozapine: a clinical review of adverse effects and management. *Ann Clin Psychiatry* 2003;15:33-48.
 13. Chong SA, Remington G. Clozapine augmentation: safety and efficacy. *Schizophr Bull* 2000;26:421-440.
 14. Buchanan RW. Clozapine: efficacy and safety. *Schizophr Bull* 1995;21:579-591.
 15. Gong QQ, Shi HZ, Wang WX. Clozapine-induced hyper-salivation and daily dosage. *J Clin Psychosomatic Dis* 1998;5:34-35.
 16. Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines Team for the Treatment of Schizophrenia and Related Disorders. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the treatment of schizophrenia and related disorders. *Aust N Z J Psychiatry* 2005;39:1-30.
 17. Chen XX, Si TM. Use of clozapine in the schizophrenia. *Clin Psychiatry China* 2007;17:394-396.
 18. Xiang YT, Wang CY, Si TM, Lee EH, He YL, Ungvari GS, et al. Clozapine use in schizophrenia: findings of the Research on Asia Psychotropic Prescription (REAP) studies from 2001 to 2009. *Aust N Z J Psychiatry* 2011;45:968-975.
 19. Carpenter WT Jr, Conley RR, Buchanan RW, Breier A, Tamminga CA. Patient response and resource management: another view of clozapine treatment of schizophrenia. *Am J Psychiatry* 1995;152:827-832.
 20. Xiang YT, Weng YZ, Leung CM, Tang WK, Ungvari GS. Clinical correlates of clozapine prescription for schizophrenia in China. *Hum Psychopharmacol* 2007;22:17-25.
 21. Harrison J, Janlöv M, Wheeler AJ. Patterns of clozapine prescribing in a mental health service in New Zealand. *Pharm World Sci* 2010;32:503-511.
 22. Chong SA, Tan CH, Khoo YM, Lee HS, Wong KE, Ngui F, et al. Clinical evaluation and plasma clozapine concentrations in Chinese patients with schizophrenia. *Ther Drug Monit* 1997;19:219-223.
 23. Van Sant SP, Buckley PF. Pharmacotherapy for treatment-refractory schizophrenia. *Expert Opin Pharmacother* 2011;12:411-434.
 24. Elkis H, Meltzer HY. Refractory schizophrenia. *Rev Bras Psiquiatr* 2007;29(Suppl 2):S41-S47.
 25. Borgio JG, Bressan RA, Barbosa Neto JB, Daltio CS. Refractory schizophrenia: a neglected clinical problem. *Rev Bras Psiquiatr* 2007;29:292-293.
 26. Conley RR, Kelly DL, Lambert TJ, Love RC. Comparison of clozapine use in Maryland and in Victoria, Australia. *Psychiatr Serv* 2005;56:320-323.