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 Li3, 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-
pine among clinicians and patients.\textsuperscript{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
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. 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. 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 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, and the less serious adverse effects of sialorrhea and weight gain. Most adverse effects of clozapine, in particular those that may be fatal, are influenced not only by treatment with clozapine but also by patient characteristics, such as age and sex, duration of illness, economic status, educational level, and clinical manifestations. Moreover, clozapine was prescribed in China, with a lower incidence than that reported in the United States and Europe. This discrepancy may be explained by racial differences in pharmacokinetic and pharmacodynamic variables.
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 clozapine 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)

| Factor                        | B     | SE    | Wald   | p   | 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                        |       |       |        |     |       |           |           |
| 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| 2.926 | 1.628     | 3.290     |
| Region (4)                    | 0.881 | 0.198 | 51.385 | 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| 2.217 | 1.383     | 3.618     |
| 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| 1.822 | 1.383     | 2.400     |
| 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†            |       |       |        |     |       |           |           |
| Educational level (1)         | 0.021 | 0.221 | 0.009  | 0.925| 1.101 | 0.662     | 1.757     |
| Educational level (2)         | 0.325 | 0.211 | 3.717  | 0.124| 1.384 | 0.916     | 2.096     |
| 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‡                   |       |       |        |     |       |           |           |
| 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 | 0.096 | 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, Shaanxi, 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 all clinicians involved in the data collection. The authors also thank clinicians who helped to organize the study in each study site.

REFERENCES

1. Nielsen J, Dahm M, Lublin H, Taylor D. Psychiatrists’ attitude towards and knowledge of clozapine treatment. J Psychopharmacol 2010;24:965-971.
2. 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.
3. Kane JM, Correll CU. Pharmacologic treatment of schizophrenia. Dialogues Clin Neurosci 2010;12:345-357.
4. Shu L. Chinese Guideline for Schizophrenia [M]. Beijing: Peking University Medical College press:2007. p.43-46.
5. 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.
6. Wu TC, Tang GR. Clinical use of antipsychotics and follow-up study. Chin J Neuropsychiat 1995;28:217-219.
7. Han QK, Ruan J. Effects of clozapine to treat the Tardive Dyskinesia. J Clin Psychol Med 2003;13:30-31.
8. 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.
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 IM. 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 Psychosomatics 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, Brie 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, Janl Boy 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 1999;21:219-223.

23. Conley RR, Kelly DL, Lambert TJ, Love RC. Comparison of clozapine use in Maryland and in Victoria, Australia. Psychiatr Serv 2005;56:320-323.