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Clozapine in schizophrenia and its association with treatment satisfaction and quality of life: Findings of the three national surveys on use of psychotropic medications in China (2002–2012)

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ABSTRACT

Objective: We examined the time trends and correlates of clozapine use in schizophrenia patients in China.
Method: A total of 14,013 patients with schizophrenia treated in 45 psychiatric hospitals/centers nationwide were interviewed in 2002, 2006 and 2012. Patients' socio-demographic and clinical characteristics including psychopathology, medication side effects, satisfaction with treatment and quality of life (QOL) were recorded in a standardized fashion.
Results: Clozapine was used in 32.9% of the whole sample; with corresponding figures of 39.7%, 32.5% and 26.4% in 2002, 2006 and 2012 ($p < 0.001$). Families of clozapine users had lower satisfaction with treatment than those of the non-clozapine group, without significant differences with respect to patients' treatment satisfaction and mental or physical QOL. In multiple logistic regression analyses, compared to the non-clozapine group, patients on clozapine had an earlier age of onset, longer illness duration, more global illness severity and drug-induced central nervous system, gastrointestinal and other side effects, lower antipsychotic doses, less delusions and hallucinations, more negative symptoms, were more likely male, inpatients, to have a family history of psychiatric disorders, receive treatments in regional centers and receive antipsychotic polypharmacy, but less likely to have health insurance and receive first-generation antipsychotics and benzodiazepines ($R^2 = 0.498$, $p < 0.001$).
Conclusions: Clozapine was used in one-third of schizophrenia patients in China, with decreasing frequency since 2002. Patients prescribed clozapine had multiple markers of greater global illness severity/chronicity and decreased satisfaction with treatment by the families, but similar QOL and less delusions and hallucinations than patients not prescribed clozapine.

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1. Introduction

Clozapine has shown to be more robustly and consistently superior to other antipsychotics (Leucht et al., 2013), particularly in patients with treatment-resistant schizophrenia (TRS) (Essali et al., 2009). Clozapine may induce agranulocytosis in rare cases (Idanpaan-Heikkila et al., 1975), therefore, it was removed from development or the market in the 1970s in the U.S. and many European countries. However, due to its unique efficacy in the treatment of TRS (Kane et al., 1988) and the introduction of regular monitoring of white blood cell count to reduce the risk of agranulocytosis, the US Food and Drug Administration (FDA) approved its use in 1990, accompanied by the implementation of a strict monitoring and dispensing system — the Clozapine National Registry (Alvir et al., 1993; Iqbal et al., 2003).

Apart from its superior efficacy in treating TRS and induction of less extrapyramidal symptoms (EPS), clozapine may reduce suicide risk (Meltzer et al., 2003) and is also effective in patients with psychotic depression (Zarate et al., 1995) or bipolar disorder (Puri et al., 1995) and may possess significant effectiveness for patients with treatment-resistant bipolar disorder (Nielsen et al., 2012). In contrast, in addition to agranulocytosis, clozapine can cause low blood pressure, sedation, serious constipation, and increase the risk of metabolic syndrome, lowering treatment adherence (Iqbal et al., 2003; Young et al., 1998). It was found that many patients discontinue clozapine in clinical practice because of its adverse effects (Mustafa et al., 2015; Young et al., 1998).

During the past decades, prescribing patterns of clozapine have been extensively examined in schizophrenia. In addition to its efficacy and adverse effects, different health care policies, socio-economic contexts, prescribing traditions and clinicians' and patients' attitudes towards clozapine have influenced its use across countries (Xiang et al., 2007). For example, while clozapine was one of the most commonly used antipsychotics in China (Si et al., 2004), clozapine had not been available in Japan until the end of 2009. Long-term observational, pharmaco-epidemiological surveys, such as the Schizophrenia Outpatient Health Outcomes (SOHO) Study (Haro and Salvador-Carulla, 2006) and the Research on Asian Psychotropic Prescription Patterns (REAP) project (Xiang et al., 2012), are important to describe the real-world use patterns and correlates of antipsychotic treatment in schizophrenia.

A national, cross-sectional pharmaco-epidemiological survey project on prescription trends for psychotropic drugs in schizophrenia was initiated by the Chinese Society of Psychiatry in 2002 (Si et al., 2004). Using data from this project, the present study aimed (1) to examine the nationwide use of clozapine in schizophrenia in three waves, in 2002, 2006 and 2012; and (2) to explore the demographic and clinical correlates of clozapine treatment and its independent associations with treatment satisfaction and quality of life (QOL).

2. Method

2.1. Study design and participants

The Chinese, national, cross-sectional pharmaco-epidemiological survey project was conducted at 45 mental health centers/units located in 10 provinces and municipalities including Beijing, Guangdong, Hebei, Hubei, Jiangxi, Jiangsu, Jilin, Shaanxi, Shanxi and Sichuan representing a range of clinical settings. The initial survey was conducted in May 2002 followed by two further surveys in May 2006 and July/August 2012 using the same design and standardized protocol. Consensus meetings on data collection and uniformity of data entry were held prior to each survey (Si et al., 2004; Zhang et al., 2012). Inpatients and outpatients treated in the participating hospitals/units during the study period of one month were consecutively screened for eligibility. All members of the research team were trained psychiatrists. The inclusion criteria were: (1) DSM-IV or ICD-10 diagnosis of schizophrenia based on a review of medical records and a clinical interview; (2) age 15 years or older; (3) taking antipsychotic drugs; and (4) the ability to understand the contents of the survey. The study protocol was approved by the Ethics Committees of the participating centers. All patients gave written informed consent.

2.2. Assessments

Basic socio-demographic and clinical characteristics were collected using a form designed for the study. Information about the types and doses of all psychotropic drugs, including clozapine, were collected from the medical records. Doses of antipsychotic drugs were converted into chlorpromazine equivalent milligrams (CPZeq) (APA, 1997; Kane et al., 1998; Woods, 2003). The cumulative doses of all antipsychotics prescribed at the time of the survey were used for analyses. Antipsychotic polypharmacy (APP) (Gallego et al., 2012a) was defined as the concurrent prescription of 2 or more antipsychotics.

In these three surveys, delusions, hallucinations and negative symptoms in the past month were evaluated and recorded during a diagnostic interview. Global illness severity was evaluated with the Chinese versions of the Clinical Global Impressions-severity scale (CGI-S) (Guy, 1976). The Treatment Emergent Symptom Scale (TESS) (National Institute of Mental Health, 1985) was used to record drug-induced central nervous system, gastrointestinal and other side effects. In the 2012 survey, patients' and their families' satisfaction with the current treatment was evaluated with a self-rated, 7-point Likert scale, scoring from 1 (extreme dissatisfaction) to 7 (extreme satisfaction). Quality of life (QOL) was assessed with the Chinese version of the Medical Outcomes Study Short Form 12 (SF-12) (Jenkinson and Layte, 1997; Zhang et al., 2011). The SF-12 is a multidimensional generic instrument with 12 items addressing eight health domains: physical functioning, role limitations due to physical problems, bodily pain, vitality, and social functioning as well as role limitations each related to emotional problems and mental health. For the purpose of statistical analysis, the first four domains were collapsed into a physical component score, while the remaining four domains formed a mental component score. A higher score on SF-12 indicates better QOL.

In China, hospitals are classified into three levels according to the degree of specialization in clinical care and research. Level-III hospitals have the highest staff–patient ratio and the best medical equipment, while Level-II hospitals are regional medical centers that treat patients with severe diseases. Level-I hospitals are small, community level hospitals providing basic medical care (Liang et al., 2004). There was no Level-I psychiatric hospital at the study time in the areas included, thus, only Level-III/II medical facilities were involved in this study.

Prior to these three surveys, all 135 raters were trained in the use of the above-mentioned instruments in 20 schizophrenia patients. The inter-rater reliability for the rating instruments between the raters yielded satisfactory to good agreement (>0.75).

2.2.1. Statistical analysis

The statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS), version 20.0 (SPSS Inc., Chicago, IL, USA). In the pooled sample, comparisons between clozapine and non-clozapine patients in terms of demographic and clinical variables were conducted using chi-square tests, independent-samples t-tests or Mann–Whitney U tests, as appropriate. Multiple logistic regression analysis with the "enter" method (i.e., all specified independent variables were entered at one time) was used to determine the demographic and clinical variables significantly associated with clozapine use. Clozapine was the dependent variable, while the variables that significantly differed between the two groups in univariate analyses were entered as independent variables.

Patients and their families' satisfaction with the current treatment and QOL were only measured in the 2012 survey. In the 2012 sample, patients and their families' satisfaction with the current treatment and QOL were compared between the clozapine and non-clozapine groups after controlling for the potentially confounding effects of variables