Cost-Effectiveness of Long-Acting Risperidone Injection versus Alternative Atypical Antipsychotic Agents in Patients with Schizophrenia in China

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ABSTRACT

Objectives: To determine the most cost-effective strategy involving first-line treatment with long-acting risperidone, olanzapine, and quetiapine from the perspective of the Chinese health-care system.

Methods: A decision analytical model was applied. The model used a horizon of 2 years. The probabilities of treatment response of different agents and the relapse and hospitalization rates were estimated by a Delphi panel of 17 senior psychiatrists in China. The unit cost for each medical service was calculated from the price system database built by China National Development and Reform Commission and the medical resource utilization was estimated by the Delphi panel. The principal efficacy measure was the proportion of patients successfully treated. Various sensitivity analyses were carried out to test the robustness of the model.

Results: The proportion of patients successfully treated over the 2-year period was 46.71% for long-acting risperidone, 39.93% for olanzapine, and 31.28% for quetiapine. The mean cost-effectiveness ratios were RMB189,427, RMB202,432, and RMB233,015 per successfully treated patient for long-acting risperidone, quetiapine and olanzapine, respectively. Results of the sensitivity analyses confirmed that the results were robust.

Conclusions: The results showed that long-acting risperidone is more cost-effective than olanzapine and quetiapine for patients with schizophrenia in long-term maintenance treatment.

Keywords: cost-effectiveness, decision tree, long-acting risperidone, schizophrenia.

Introduction

Schizophrenia is a very serious mental illness [1] and is one of the most expensive illnesses to treat [2]. A recent systematic review of 158 studies found a median incidence rate of 15.2 per 100,000 [3]. Schizophrenia is also among the top 15 leading causes of disability and the top 10 leading causes of years lost due to disability [4]. Empirical results from the reviewed studies indicate that the negative economic consequences of mental illness far exceed the direct cost of treatment, thus making it important to treat mental illness [5]. In China, there are about 16 million patients suffering from mental disorder [6] and almost half of them are attributed to schizophrenia [7]. It is estimated that the annual economic cost of schizophrenia exceeds RMB11 billion [8].

Relapse is the primary cost driver in schizophrenia and is closely related to levels of adherence to therapy [9]. Both atypical antipsychotic agents and depot preparations have been shown to be useful in improving therapeutic adherence and cost saving compared with oral conventional antipsychotic agents [10,11]. Long-acting risperidone is a new formulation of an atypical antipsychotic agent that combines the pharmacological advantages of the atypical drugs with those of a long-acting injectable formulation, and has been shown to be efficacious in short- and long-term clinical trials by improving the patients’ compliance and reducing relapse (For details, see Cost-Effectiveness of Long-Acting Risperidone Value in Health Supporting Information, Part 1 at: http://www.ispor.org/Publications/value/ViHi2s3_Ming.asp.) [12,13]. The improved compliance compared with existing treatment regimens implies that the higher acquisition costs should be partially offset by reduced rates of relapse. However, the long-acting injectable formulation has not been widely used in China; only 61.8% of all patients with schizophrenia use atypical antipsychotic agents and 6.5% use depot antipsychotic medications in 2002 [14].

Despite the differences in costs and reimbursement structures of the different health-care systems, a consistent overall conclusion emerged from the different models that compare long-acting risperidone with other oral atypical or conventional depot antipsychotic agents: long-acting risperidone reduces relapses and is, thereby, cost saving [15-24]. However, there is limited research on the cost-effectiveness of long-acting risperidone compared with other treatment strategies in China.

Therefore, the aim of the present pharmacoeconomic evaluation is to determine the most cost-effective pharmacological treatment strategy for schizophrenic patients from three clinically relevant options.

Methods

A decision tree model was created to compare the cost-effectiveness of three first-line treatment strategies in a sample of young schizophrenic patients. It was carried out from the perspective of the Chinese health-care system over a 2-year period. The study was conducted by an expert committee made up of 11 senior psychiatrists, two pharmacoeconomists, and a health economics expert from Xian-Janssen Pharmaceutical. The role of the expert committee was to develop and validate a methodology for use in this pharmacoeconomic assessment. Specifically, this committee decided on the model type, target group (patient population), effectiveness criteria, types of costs, clinical outcomes, and variables to be tested in the sensitivity analyses.

Model Structure and Study Design

The decision tree model has three main branches corresponding to the therapeutic strategies: long-acting risperidone injection,
oral olanzapine, and oral quetiapine. Patients entering the model are defined by the expert panel as a group of stable schizophrenic patients who met the Diagnostic and Statistical Manual of Mental Disorders criteria for schizophrenia or schizoaffective disorder, between 20 to 45 years old, treated for at least 1 year, and whose disease had not been diagnosed for longer than 5 years and it has the best therapeutic potential (For details, see Part II at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Ming.asp) [21,23].

The model structure was based on a model by De Graeve et al. [21] and Yang et al. [23]. A time horizon of 2 years, divided into six periods of 4 months each, was chosen. If the patient did not respond to the therapy after 4 months of treatment, an alternative therapy was proposed. A patient could receive four different treatments before long-term hospitalization occurred. The reappearance of positive symptoms, delusions, suicidal ideation, or behavioral problems may prompt their physicians to make a therapeutic change. The order of therapeutic changes among the three different treatments was determined by the expert committee (Table S1; see Part III at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Ming.asp).

Clozapine is regarded as an atypical antipsychotic agent for use only as second-line or subsequent treatment in China. Therefore, in this study, it could only be offered as the fourth choice in a sequence.

**Definition of Health States and Efficacy Criteria**

The principal efficacy measure was the proportion of patients successfully treated, defined as those who responded to initial treatment and who had no more than two episodes of clinical deterioration and did not need a change of treatment, over the 2 years [21,23].

Three different health states, clinical response, clinical deterioration (CD), and inadequate response (IR), were defined by the expert panel, similar to the Taiwan study (Fig. S1; see Part IV at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Ming.asp) [23].

The incidence of extrapyramidal side effects (EPS) and dosage of each strategy in different mental states were determined by the expert committee, who gave consensus estimates based on literature review and on their own clinical experience (Table S2; see Part V at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Ming.asp).

**Data Sources**

Information on therapeutic choices, transition probabilities between health states, and the incidence of side-effects was obtained from a 17-member expert panel of Chinese psychiatrists (Delphi method) (for details, see Part VI at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Ming.asp). Two rounds of surveys were conducted in this Delphi panel. Only minor fluctuations of the parameter values were observed after the second-round response.

The costs of the three states of response, CD, or IR were estimated from the perspective of the Chinese health-care system. We assumed that all patients in the target group should receive psychiatric intervention during the 2-year period. The psychiatric intervention included outpatient visit, emergency treatment, emergency observation, day hospital, and hospitalization. The unit cost for each medical procedure was calculated from the price system database built by the China National Development and Reform Commission and the utilization of five different psychiatric interventions in each health state was acquired from the 17-member Delphi panel. The cost of treating extrapyramidal effects was added for all strategies, with the mean daily treatment cost calculated on the basis of drug prescription data and using the doses reviewed by the expert panel. All costs were discounted at a rate of 3%.

**Sensitivity Analysis**

A decision analysis model was created using TreeAge Pro 2007 (TreeAge Software Inc., Williamstown, MA), which calculated mean cost-effectiveness and incremental cost-effectiveness ratio for each of the three treatment strategies. The C/E was expressed as the cost per successfully treated patient. Two variables, price of long-acting risperidone and the range of discount rate for costs from 0% to 10%, were tested using one-way sensitivity analysis.

**Results**

**Efficacy and Cost**

Excluding medication cost, the average cost of outpatient visits and emergency treatment were RMB177.62 ± 188.39 and 177.94 ± 129.66 (currently, SUS1 = RMB6.8), respectively. The average costs for emergency observation, day hospital, and hospitalization per day were RMB291.92 ± 158.13, RMB80.35 ± 39.50, and RMB691.64 ± 628.53, respectively. The costs of the three states of response, CD, or IR for a 4-month treatment were RMB2577.92, RMB7061.29 and RMB12980.95, respectively.

Analysis of the response rate after 2 years of treatment found that long-acting risperidone was the most effective strategy, with 46.71% of patients successfully treated after 2 years of treatment, compared with 39.93% for olanzapine and 31.28% for quetiapine. The mean cost per patient over 2 years was RMB88,483 for long-acting risperidone, RMB93,055 for olanzapine, and RMB63,314 for quetiapine. And the mean C/Es were 46.71% of patients successfully treated after 2 years of treatment, compared with 39.93% for olanzapine and 31.28% for quetiapine.

**Sensitivity Analysis**

The hypothesis was tested in the range of discount rate from 0% to 10%. In each scenario, long-acting risperidone completely dominated both the oral olanzapine and quetiapine strategies (Fig. S2; see Part VIII at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Ming.asp).

A sensitivity analysis of drug prices was also performed. Assuming that the price of long-acting risperidone was decreased or raised by 2%, 4%, 6%, 8%, or even 10%, long-acting risperidone still emerged as the most cost-effective strategy (Fig. S3; see Part IX at: http://www.ispor.org/Publications/value/ViHsupplementary/ViH12s3_Ming.asp).

**Discussion**

Schizophrenia is a severe and chronic illness as well as one of the most expensive illnesses to treat. Relapse and rehospitalization contribute significantly to the economic burden of schizophrenia. It is known that the relapse rate is 80% if a patient discontinues his/her antipsychotics for more than 2 years [25]. Partial compliance with antipsychotic medication is associated with an increased risk of inpatient hospitalization [26]. Health care resource use is significantly reduced in patients with stable schizophrenia receiv-
ing depot formulation [26]. However, the high incidence of tardive dyskinesia for conventional antipsychotics remains as the main drawback for using conventional depot formulation in treating schizophrenia [26]. The long-acting risperidone is an innovative medicine that presents advantages not only improving compliance but also decreasing the adverse effect that leads to more reductions of health-care resource and costs.

Previous cost-effectiveness analyses of long-acting risperidone compared with oral olanzapine and haloperidol depot have shown significant cost savings associated with risperidone due to improved efficacy, and in particular, fewer EPS [16–23]. Those results cannot be generalized for China, where the treatment modalities and costs are different. Currently, the Positive and Negative Syndrome Scale is often used to measure the efficacy of antipsychotics in China [14]. Haloperidol depot is not widely used in China because of high incidence of EPS, and oral olanzapine and quetiapine are the main alternative options to long-acting risperidone among the new generation of antipsychotics for schizophrenia [14]. No study has been conducted to date to compare the benefits of long-acting atypical antipsychotics with those of other atypical antipsychotics in China. Therefore, this model simulation fills an important literature gap in China in this regard.

We used an estimation method similar to that of a Belgian study that used a simple decision tree as a model for the therapeutic management of schizophrenia [21]. Available literature cannot supply all the data that are necessary to construct a decision tree. As an alternative, an expert committee and randomly selected psychiatrists provided estimates of the effectiveness indicators for the models. All of our analyses showed that the C/E of long-acting risperidone was lower than those of olanzapine and quetiapine. The robustness of the analytical model was also validated by varying the price of long-acting risperidone and the discount rate.

It is known that, in patients with schizophrenia, the total health-care expenditure (including direct and indirect costs) is significantly higher than mental care cost alone [5]. However, it is very difficult to measure all direct medical and non-medical costs for each of these medical problems, and loss of work day induced by antipsychotics in China. Therefore, other than costs for EPS, medical costs for other side effects of antipsychotics, such as weight gain, sexual dysfunction, endocrine dysfunctions, and cardiovascular problems, indirect cost such as productivity loss were omitted. Thus the present cost figures are underestimates of the actual costs of each strategy.

Another limitation of the study is the fact that the decision tree analytical method inevitably runs the risk of simplifying a complex reality. Patient response over different time frames is indeed more complex in real life than in the choices portrayed in this study. However, we believe that the decision times and response patterns reasonably approximate this very complex reality, as validated by an expert committee [21]. Similarly, the assumption that long-term hospitalization would occur after four therapeutic failures is based on the expert committee’s opinion. Thus the results need to be confirmed by a prospectively designed study. Third, the study population, defined as stable patients with schizophrenia who were thought to be more responsive after antipsychotic treatment, was a limited group of patients. Therefore, caution must be taken before generalizing the results to all patients.

Conclusion

The present study adds to a growing body of literature supporting the favorable cost effectiveness of long-acting risperidone for the management of schizophrenia. All of the analyses showed that the C/E of long-acting risperidone was lower (more cost-effective) than those of olanzapine and quetiapine. Results of the sensitivity analyses confirmed the robustness of the model. The authors gratefully acknowledge the sponsorship funding provided by Xian-Janssen Pharmaceutical Ltd.

Source of financial support: Xian-Janssen Pharmaceutical Ltd.

Li Yang, Ming Li, Li-bo Tao, Mingliang Zhang, Deborah Nicholl, and Peng Dong have no conflicts to declare.

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