Health Decision

ORIGINAL ARTICLE

Cost effectiveness analysis of blonanserin *versus* ziprasidone as first-line treatment for patients with schizophrenia in China

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ABSTRACT

Background and Objectives: The aim of the study is to evaluate the cost-effectiveness of blonanserin compared with ziprasidone as first-line treatment for patients with schizophrenia in China. **Methods:** A 10-state Markov model was built to assess the long-term cost-effectiveness of blonanserin from China health care system perspective. A time horizon of 10 years with monthly cycle was chosen. Patients with schizophrenia will receive blonanserin or ziprasidone as first-line treatment and could switch to olanzapine or clozapine as second-line or third-line treatment when symptoms relapse happens. Efficacy and safety data were derived from network meta-analysis. Probabilities of experience recurrences were derived from a retrospective cohort study. The costs were obtained from real world data and local published resources. Costs and outcomes were both discounted at 5%. Sensitivity analysis were conducted to verify the robustness of the results. **Results:** Blonanserin generated 4.30 quality-adjusted life-years (QALYs) with cost of Chinese Yuan (CNY) 167,011, whereas ziprasidone generated 4.28 QALYs with cost of CNY 173,575. Compared with ziprasidone, blonanserin was seen as the dominant treatment. One-way sensitivity analysis demonstrated the robustness of the base case results. Probabilistic sensitivity analysis showed that blonanserin was a cost-effective strategy in more than 70% simulations under the local threshold compared with ziprasidone. **Conclusions:** Compared with ziprasidone, blonanserin is cost-effective as first-line treatment for patients with schizophrenia in China.

Key words: cost-effectiveness analysis, schizophrenia, blonanserin, ziprasidone

INTRODUCTION

Schizophrenia is a kind of severe mental disorder affecting patients' perceptions, thoughts, moods, and behaviour. It has a long-term burden to patients, the caregivers, and their families. According to the data from Global Health Data Exchange (GHDx), the prevalence of schizophrenia in China, the United States, Australia, Germany, Japan, and India were 0.39%, 0.49%, 0.44%, 0.33%, 0.31% and 0.29% in 2019, respectively. Compared with other Asia or European countries, China has a relatively high prevalence of schizophrenia. Schizophrenia also brings about significant financial burden. A study in Guangzhou, China estimated that the average direct medical costs was 41,972.4 Chinese Yuan (CNY) (6852.5 United States Dollar [USD]) per patient per year while the non-medication costs accounted for the biggest part.[1] Also, the caregivers living with patients face with significant emotional burden in China.[2]

Due to the heavy burden of schizophrenia, the therapies to control the disease episodes, improve the symptoms

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and prevent the relapse are important. First generation antipsychotics (FGAs) such as chlorpromazine and perphenazine are seldom used recent years due to the adverse effects. Whiles second generation antipsychotics (SGAs) such as risperidone, olanzapine, ziprasidone with fewer side effects show better efficacy on both positive and negative symptoms of schizophrenia and was recommended by the guidelines as a priority.[3–5]

Blonanserin is a new SGA that selectively blocks 5-HT2 and D2 receptors. Several randomized double-blind studies in Japan, Korea and China demonstrated that blonanserin has a greater beneficial effect on the negative symptoms of schizophrenia patients than does haloperidol. Compared with haloperidol and olanzapine, blonanserin has fewer incidences of prolactin increasing and extrapyramidal symptoms (EPS).[6–9] Blonanserin has been approved of treat schizophrenia patients and was included in the National Reimbursement Drug List (NRDL) in China already.

Though both recommended by guidelines as first line treatment and used widely in China, there were not any published economic evaluation to compared blonanserin with ziprasidone. This study aimed to assess the cost-effectiveness of blonanserin compared to ziprasidone in China and provided advice for clinical and health insurance decisions.

METHODS

Analytic overview

The base case intention-to-treatment (ITT) population in the model was Chinese adult patients with schizophrenia treated by blonanserin (BLO) or ziprasidone (ZIP) as first-line therapy. The perspectives of the research were from the health care system perspective. Both costs and outcomes were discounted at 5% per annum. Effectiveness was assessed in the analysis in terms of quality-adjusted life-years (QALYs). The primary economic endpoint is the projected lifetime incremental cost per QALY gained incremental cost-effectiveness ratio (ICER).

Model structure

According to the published cost-effectiveness analysis,[10–12] a 10-state Markov model with 4-week cycle, to reflect the chronic nature of the disease, was constructed in Microsoft Excel to estimate the effectiveness (relapse, discontinuations, adverse events and mortality) and costs for adult patients with schizophrenia (Figure 1). Health states of model included, "non-stable", "stable while adherent", "stable but non-adherent", "relapse" and "death" according to previous published models of schizophrenia. A 10-year time horizon was used to reflect longer-term differences between treatments and the half-cycle correction was applied.

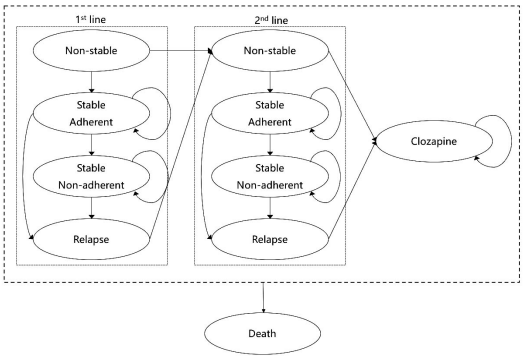

Figure 1. Model structure.

The assumptions of model included: (1) treatment is initiated in a population with acute schizophrenia (acute phase), who then moved to a stable phase following disease or switch to 2nd-line treatment; (2) both patients in the BLO arm and the ZIP arm would receipt olanzapine (OLA) as 2nd-line treatment when they relapsed or failed with 1st-line treatment; (3) all patients would switch to clozapine (CLO) when relapsed or failed with olanzapine; (4) patients who have not discontinued treatment by week 4 were assumed to enter the stable/adherent state and were assumed initially to be on treatment; (5) patients discontinuing treatment at the week 4 for any reason were assumed to switch to the next line treatment (olanzapine or clozapine); (6) patients discontinuing their treatment in the "stable phase" were assumed to receive no therapy, and stayed in the stable/non-adherent state until the onset of relapse; (7) patients who relapse were assumed to discontinue current therapy and switch to the next therapy in the sequence; (8) Patients could die of any health state within the model. The structure and assumptions of this model were approved by several clinical experts in China; (9) Patients were 34 years old when entered the Markov model according to the China clinical trial of blonanserin.

Model inputs

Clinical efficacy

The main clinical inputs in this model were the probabilities of all-cause discontinuation of patients in the non-stable state and the stable/adherent state. The all-cause discontinuation of patients treated with blonanserin in the non-stable state was derived from a double-blind, parallel-group multicenter randomized trial carried out in China. Considering there were not any head-to-head clinical trials compared blonanserin, and ziprasidone, a net-work meta-analysis was conducted to derive odds ratio to calculate the all-cause discontinuation of patients treated with ziprasidone or olanzapine in the non-stable

state (Table 1). The detail of the network meta analysis (NMA) could be found in the supplements. The clinical trial and the net-work meta-analysis could only show the short-term clinical outcomes. For the stable phase, long-term risks of relapse and all-cause discontinuation for blonanserin, ziprasidone and olanzapine were taken from a retrospective cohort study. This retrospective cohort study reported the Kaplan-Meier (KM) curves to describe the time-dependent all-cause discontinuation of different treatment. To extrapolate beyond the observation period, multiple parametric distributions–exponential, Weibull, log-normal, gamma, log-logistic, and Gompertz–were fit to the K-M curves.[13,14] After assessing goodness-of-fit using the Akaike information criterion (AIC) and the Bayesian information criterion (BIC), the log-normal distribution was chosen for patients treated with blonanserin, the Gompertz distribution was chosen for patients treated with ziprasidone, and the exponential distribution was chosen for patients treated with olanzapine. The model included the all-cause discontinuation of non-adherent patients, the dead patients and the relapsed patients. According to clinical experts' opinions, about 20% of patients who discontinued treatment transferred into relapse state, which was used to calculate the translation probability from the stable/adherent state to the relapse state. Moreover, the relapse rate of patients in the stable but non-adherent state was taken from a published literature about compliance with antipsychotic treatment and relapse in schizophrenia (Table 2).

Table 1: Summary of net-work meta-analysis (odds ratio of BLO *vs.* ZIP)

	Value	Range
All-cause discontinuation in non-stable state	0.75	0.33~1.75
Weight gain	0.64	0.06~5.04
EPS	1.15	0.41~3.07
Prolactin increasing	1.30	0.20~8.10

BLO: blonanserin; ZIP: ziprasidone; EPS: Extrapyramidal symptoms.

Based on the clinical experts' opinions, the main adverse events (AEs) in the model included weight gain, EPS and prolactin increasing. All incidence of AEs was derived from the China clinical trial of blonanserin *versus* ziprasidone and the network meta-analysis (Table 3).

Mortality was based on published life tables of the general population and adjusted to reflect the increased risk of mortality in patients with schizophrenia.

Health state utilities

Each health state was assigned a health utility score based on the data collected from published literature. In this model, we assumed that the utilities were only related to health states rather than therapies. Disutilities associated with AEs were estimated based on established values in the literature. Patients in the clozapine-treated state would not calculate any disutilities as the utility treated with clozapine was including the disutilities of all AEs.

Table 2: Summary of clinical inputs used in the model

Rate	Value
All-cause discontinuation of blonanserin in non-stable state[6]	3.95%
All-cause discontinuation of ziprasidone in non- stable state	3.81%
All-cause discontinuation of olanzapine in non-stable state[6,8]	2.12%
Proportion of patients who discontinued treatment transferred into relapse state[6,15,16]	20%
All-cause discontinuation of blonanserin in stable state[17]	Log-Normal distribution: constant = 1.76, θ = 1.96
All-cause discontinuation of ziprasidone in stable state[17]	Gompertz distribution: constant = -1.57, γ = -0.12
All-cause discontinuation of olanzapine in stable state[17]	Exponential distribution constant = -2.80
Relapse rate of non-adherent[18]	6.27%
Increased risk of mortality[19]	2.6
Weight gain of blonanserin[6]	7.17%
Extrapyramidal symptoms of blonanserin[6]	28.21%
Prolactin increasing of blonanserin[6]	30.94%
Weight gain of ziprasidone	12.45%
Extrapyramidal symptoms of ziprasidone	28.95%
Prolactin increasing of ziprasidone	61.30%
Weight gain of olanzapine[6,20]	25.33%
EPS of olanzapine[6,20]	13.85%
Prolactin increasing of olanzapine[6,20]	0.01%

Table 3: Summary of utility inputs used in the model

State	Value	Range
Non-stable state[21]	0.575	0.526~0.624
Stable/adherent state[21]	0.933	0.892~0.974
Stable/non-adherent state[22]	0.740	0.630~0.850
Relapse[21]	0.575	0.526~0.624
Clozapine-treated state[22]	0.260	0.190~0.340
Weight gain[21]	-0.089	-0.118~-0.060
Extrapyramidal symptoms[21]	-0.256	-0.299~-0.213
Prolactin increasing[21]	-0.089	-0.116~-0.062

Costs

The analysis included the costs of drugs, drug administration, management of adverse events, state-specific supportive care, and hospitalization. All costs were

estimated in Chinese Yuan and adjusted to 2022.

The unit prices of the medical resources used therapeutic process were based on the data of governmental publications and the database's name is MENET database.

The costs of follow-up were estimated based on the unit price and frequency of examination items. The kinds and frequency of examination items used for patients were recommended by Chinese clinical experts (Table 4) .

The mean cost of AEs for each arm was estimated by multiplying the probability of adverse events by the cost of managing each AE. The costs of managing AEs were obtained from the real-world data in China.

All cost inputs assumed to increase or decrease by 25% in the one-way sensitivity analysis. A summary of cost inputs used in the model is showed in Table 4.

Sensitivity analyses

Sensitivity analyses were performed to determine which variables, when varied, would have a substantial impact on projected costs and outcomes. We presented one-way sensitivity analyses using tornado diagrams (Figure 2). We also performed a probabilistic sensitivity analysis using Monte Carlo simulation to further test the robustness of the results.

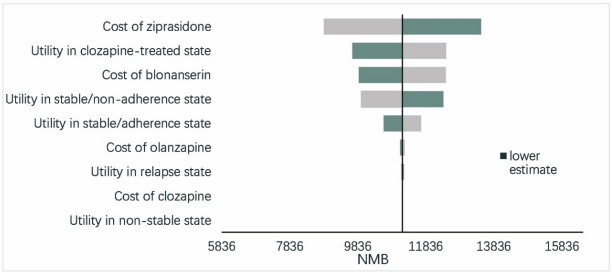

Figure 2. Tornado diagram. NMB: net money benefit.

RESULTS

Base case analysis

Table 5 shows the detailed results of the base case analysis. According to the simulation of the Markov model, the blonanserin arm provided 4.30 QALYs at a cost of CNY 167,011, whereas the ziprasidone arm provided 4.28 QALYs at a cost of CNY 173,757. Thus, compared with ziprasidone, patients with schizophrenia treated with blonanserin as 1st-line therapy could gained 0.02 QALYs and save CNY 6746, which means blonanserin was the cost-effective choice.

Sensitivity analyses

The results of the one-way sensitivity analyses are presented in the tornado diagram (Figure 2). The net money benefit (NMB) was calculated using three times the gross domestic product (GDP) per capita of China in 2022 as the threshold of willingness-to-pay (WTP). The parameters with the greatest influence on the NMB were utilities in the different states, costs of different drugs. Across broad variation in the ranges for each parameter, the NMB was above 0, which proved the robustness of the results.

The results of the probabilistic sensitivity analyses were reported as the cost-effectiveness acceptability curves (CEAC) in Figure 3. These curves showed the probability that the probability that the blonanserin arm was cost-effective across increasing WTP values was above 70% probability when the threshold was three times the GDP per capita of China, which was the same as the results of the base case analysis.

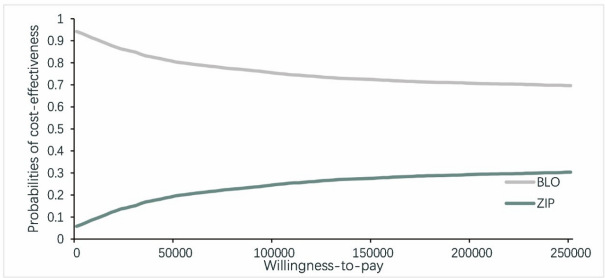

Figure 3. Cost-effectiveness acceptability curves. BLO: blonanserin; ZIP: ziprasidone.

DISCUSSION

SGAs was recommended for patients with schizophrenia by guidelines. According to a published economic evaluation in China, ziprasidone could be a cost-effective choice when compared with risperidone, olanzapine, quetiapine and aripiprazole from a short-time simulation. As a new kind of SGA, several randomized controlled trials (RCTs) showed blonanserin had a good performance in terms of safety and efficacy, especially in the aspect of reducing incidence of weight gain and increased prolactin.[23] However, there lacks sufficient economic evaluation evidence about blonanserin compared with ziprasidone in China. Besides efficacy and safety, the cost-effectiveness would be an important indicator for SGAs selection for long-term anti-schizophrenia treatment. From a systematic review of economic evaluations for the treatment of schizophrenia, most of the quality of Chinese economic evaluations was relatively low dues to the short time horizon or non-QALY outcomes and may introduce confusions for decision makers. This study, as the first

Table 4: Summary of follow-up inputs used in the model

Item	Unit cost (¥)	Frequency		Costs per cycle (¥)	
		Non-stable	Stable	Non-stable	Stable
Doctor service	25.6	1	1 per week	25.60	102.40
Blood test	19.2	1	1 per 3 weeks	19.20	6.40
Urine test	4.5	1	1 per 3 weeks	4.50	1.50
Blood biochemistry	299.29	1	1 per 3 weeks	299.29	99.76
Hormone test	197.79	1	1 per 3 weeks	197.79	65.93
Electrocardiograph	16.925	1 per week	1 per week	67.70	67.70
Thyroid function test	137.5	1	1 per 3 weeks	137.50	45.83
PANSS checklist	39.5	1 per week	0	158.00	0

PANSS: positive and negative syndrome scale.

Table 5: Summary of cost inputs used in the model

Item	Unit price (¥)	Dose per day	Cost (¥)
Blonanserin	46.80/40 mg	8 mg	9.36 per day
Ziprasidone	131.23/400 mg	50 mg	16.40 per day
Olanzapine	14.88/10 mg	12.5 mg	18.60 per day
Clozapine	12.90/2500 mg	200 mg	1.03 per day
Hospitalization	-	-	66.31 per day
Extrapyramidal symptoms	-	-	701.23 per cycle
Prolactin increasing	-	-	1044.74 per cycle

cost-effectiveness analysis of blonanserin *versus* ziprasidone as the 1st-line treatment for Chinese patients with schizophrenia, modelled the long-term results of health outcomes and direct medical costs through a complicated Markov model proved by clinical experts to provide high quality evidence to decision makers.[24] In our base case analysis, compared to ziprasidone, blonanserin is a dominant strategy, as using blonanserin associated with an overall 10-year cost saving of CNY 6746 and an increase of 0.02 QALYs per patient. Sensitivity analyses suggested that the cost-effectiveness of blonanserin *versus* ziprasidone was robust. Probabilistic sensitivity analysis further supported the base-case results, demonstrating that blonanserin has an above 70% probability of being cost effective at the willingness-to-pay thresholds in China. Based on this study, compared with ziprasidone, blonanserin could be a better choice because of lower costs and higher outcomes both for patients and China medical insurance fund from a long-term perspective.

There are several strengths to this economic analysis. Due to the chronic nature of schizophrenia and the long-term effects of the condition,[10,11,25–27] the implementation of a Markov model and a 10-year time horizon allow the long-term assessment of cost-effectiveness and is in line with the published models. As the most influence parameter, the probabilities of all-cause discontinuation in the stable state were calculated using survival analysis allowing the probabilities to change with time. This could be more in line with the reality. Regardless of the certain number of the assumptions in the model, all the assumptions were proved by clinical experts to ensure that the study designs comply with clinical practice in China.

There are some limitations in the study. First, due to the absence of direct non-medical costs and indirect costs, this cost-effectiveness analysis was carried out from the health care perspective. While in fact, schizophrenia affects not only the patients but also their family and the society. Thus, the cost-effectiveness analysis of schizophrenia was more suitable to be carried out from the society perspective. This study from healthcare system perspective may underestimate the benefits of treatment with blonanserin. Second, the efficacy data sources in the non-stable state and the stable state, which were derived from different studies and the reliance on an indirect comparison of blonanserin *versus* ziprasidone would cause research bias.

CONCLUSION

From a Chinese healthcare system perspective, blonanserin as first-line treatment is a cost-effectiveness option for patients with schizophrenia in China comparing to ziprasidone, which is yield more QALY gains with lower costs.

DECLARATION

Author contributions

Guan X conducted the Markov model, cost-effectiveness analysis and drafted the manuscript. Wang L modified the Markov model and revised the manuscript. Cao Y, Shi F and Xu H seaeched literatures and extracted data. Ding J and Wu M helped with data management and manuscript revision. Li H designed this study and helped with manuscript preparation and revision.

Ethics approval

Not applicable.

Source of funding

This study was supported by Sumitomo Pharma (Suzhou) Co., Ltd.

Conflict of interest

Jie Ding and Meiyu Wu worked for Sumitomo Pharma (Suzhou) Co., Ltd. This article was financially supported by company, but subject to the journal's standard procedures and peer review process. The other authors declare no competing interest in this publication.

Data availability statement

Not applicable.

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