Olanzapine versus Haloperidol in the Treatment of Refractory Schizophrenia: A Cost-Effectiveness Analysis

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Abstract

Objective This study intends to introduce a model of cost-effective analysis by comparing olanzapine with haloperidol, which is the conventional treatment in refractory schizophrenia.

Method Data from clinical trials were used to compare olanzapine with haloperidol in patients with refractory schizophrenia. Outcomes were compared among direct and indirect cost with the view point of health care provider at Ramathibodi Hospital and society in one year of treatment by path analysis and cost analysis, sensitivity analysis was shown for clinical decision when there is some cost or path probability have been changed so the decision will be changed at some threshold to another alternative.

Results The total cost of olanzapine treatment to get one healthy of refractory schizophrenia is 668,928.0 Baht per year. On the other hand the total cost for haloperidol is 1,565,337.8 Baht per year. Olanzapine provides net benefit to one by 896,409.8 Baht per year. In the sensitivity analysis showed that olanzapine will always provide this advantage as long as the response rate of olanzapine is more than 21.5%. Haloperidol will provide the same cost effective to the patient if its response rate is better than 27.5%.

Conclusions The result of this economic evaluation suggests that the total one year cost of treatment by olanzapine appears to be more effective than haloperidol in the treatment of TRS. This is the impact of the cost reduction of medical care for TRS patients during one year of treatment. **J Psychiatr Assoc Thailand 2000; 45(1): 71-85.**

Key words : cost effectiveness, refractory schizophrenia, olanzapine, haloperidol, sensitivity analysis

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Introduction

Schizophrenia is a severe chronic mental illness affecting approximately 20 million people worldwide with lifetime prevalence rate 1 %[1]. It places a major economic burden on society, in terms of both direct and indirect cost. The total cost of schizophrenia[2] in 1990 in the USA were estimated to be $US32.5 billion, with 53% of this amount comprising direct medical cost , 37% lost productivity due to morbidity and premature mortality, and 10% were other cost such as those attached to family caregivers' time. The amount of direct medical cost was an average of $US4100 per patient per annum.

Conventional neuroleptic therapy reduces acute psychosis and recurrence rates. However, approximately 30% of patients do not respond. Neither did it exert therapeutic effects against all domains of schizophrenic pathology, e.g. negative or deficit features[3]. Equally important, conventional antipsychotics carry side-effects such as extrapyramidal symptoms (EPS), tardive dyskinesia (TD), neuroleptic malignant syndrome (NMS) which compromise patient compliance. Furthermore, in the NIMH study the relapse/recurrence rate in the neuroleptic responder group was as high as 78% during 2-12 years of follow up period[4]. The care of these patients is further complicated by the issue of treatment-refractory schizophrenia (TRS).

Clozapine therapy is the best established treatment for TRS, with a response rate of about 30-50 %[5]. Unfortunately, those who benefit often manifest marked psychopathology, and many TRS patients are unable to take clozapine for a variety reasons[6] especially due to increase risk of agranulocytosis.

The present study's aim is to search for other antipsychotic agents with more benefit. Alternative approaches, implicating other neurotransmitter systems, have led to the development of novel antipsychotic candidates[7]. A prototype is olanzapine, a thienobenzodiazepine. Biochemical studies have demonstrated that olanzapine has a broad pharmacological profile with high affinity for serotonin$_{2A/2C}$, dopamine D_1, D_2, muscarinic, alpha$_1$ adrenoreceptors, and histamine H_1 receptors[8]. Recently, Seeman[9] reported that olanzapine, like clozapine, has high affinity for the dopamine D_4 receptor and that an action at this receptor may contribute to the pharmacological profile of the compound.

Olanzapine has been currently introduced in Thailand but the cost of the drug was very high compare to conventional antipsychotics. So its efficacy and low side effect had to be weighed with its cost, particularly in the country like Thailand where resources of health care is highly limited. We therefore carried out this study to compare olanzapine with the conventional antipsychotic (haloperidol) in TRS by cost effectiveness analysis. Schizophrenia[10] is a chronic disease, it is a life long treatment for most patients especially those with TRS. One year period of treatment was used for our economics analysis because it will cover the response period of the drugs about 4-8 weeks and the relapse or the complication such as suicide which occur usually within one year.

The results of this pharmacoeconomic studies will help clinicians and health care policy makers to determine which treatment will provide the most benefit to TRS in term of patients' functioning and well-being at the most acceptable medical cost.

The objectives of the study were to determine the cost-effectiveness (in Baht, 1998) of olanzapine (OLZ) in the treatment of patients with refractory schizophrenia compared to haloperidol (HAL) in the

view point of health care provider and society, and to perform the sensitivity analysis of the main variables that affected the analysis.

Study design

This is an economic evaluation study using a clinical decision analysis model. Parameter estimations were based on the information through literature reviews on clinical trial data, published medical literature and, when need, clinical judgment in the treatment of refractory schizophrenia from the perspectives of health care provider and the society.

Operational definition

Refractory schizophrenia: The criteria used in this study were the original clozapine trials and were adapted from Kane et al[11]. The criteria were:

1) patients with schizophrenia had to have failed in the current episode at least 2 distinct periods of neuroleptic treatment for at least 2 different classes,

2) the duration of each neuroleptic treatment at least 6 weeks without symptom relief,

3) the dosage of previously failed neuroleptics must have been more than 750 mg/day chlorpromazine equivalence,

4) there were no period of substantial relief of symptom as evidence from Brief Psychiatric Rating Scale (BPRS) >35, and

5) the duration of illness must be more than 2 years.

Critical review

A single, global, Phase III protocol was conducted in 17 countries involving 178 investigative sites[12]. Nineteen hundred and ninety-six patients were randomized to either OLZ (5 to 20 mg) or HAL (5 to 20 mg). More patients completed six weeks of acute pharmacotherapy with olanzapine (66%) than with haloperidol (47%) statistically significant due to the compliance and the side effect from the drugs. While comparable reduction in BPRS-positive symptoms (baseline to endpoint) was observed for OLZ and HAL, the former was statistically significantly superior on the following efficacy parameters: BPRS total, BPRS negative symptoms, PANSS (Positive and Negative Symptom Scale) negative, and CGI (Clinical global impression) severity. Baseline to endpoint improvement in depression also favored OLZ. Furthermore, OLZ was associated with a statistically significant lower incidence of EPS. Significantly greater baseline to endpoint reduction in Simpson-Angus Rating Scale score was also observed.

Davies and Drummond[13] estimated the relative cost-effectiveness of clozapine and standard antipsychotic agents in the management of TRS within the National Health Service. A decision analysis model was designed on the basis of the study by Revicki et al[14] and supplemented by additional data sources. The authors concluded that clozapine would be no more expensive, and possibly less expensive, than standard antipsychotic therapy in TRS within a realistic range of assumptions employed in the model.

Almond et al[15] valued the parameters and outcome scores derived mainly from an international clinical trial with the result a comparison of the 2 drugs is approximately cost equal.

Sacrist and Gome[16] had reviewed the rate of response to OLZ with TRS 36%-48%. It was suggested that OLZ may be effective in a significant number of neuroleptic-resistant schizophrenic patients and the efficacy obtained did not necessarily imply an increase in the cost of the treatment.

From Marder's report[17] the rate of response of HAL for TRS was only 12% .

The side effects of these two drugs were reviewed thoroughly in the study of Casey[18] and were used in this current study both parameters and the side effect probability.

From the study of Hamilton et al[19] there were 14 fewer hospital days per year of treatment exposure in olanzapine-treated patients compared with haloperidol-treated patients.

Over a 5-year period, patients on OLZ had an additional 6.8 months in a disability-free health state based on BPRS and more than 2 additional months in a disability-free health state based on quality-adjusted life years, and they experienced 13% fewer relapses compared with patients on HAL[20].

Suicide is the most common form of death among schizophrenic patients and occur in 10%-15%[21]. OLZ has been proved to reduce the suicidal rate among the response more than HAL.

Economic evaluation

Description of the alternatives

Alternative 1 ; Olanzapine (OLZ) for TRS for one year review all the direct and indirect cost with the health care provider and society perspective.

Alternative 2 ; Haloperidol (HAL) for TRS for one year which is the conventional treatment with the same analysis as alternative 1.

Outcome measurement

1. The psychiatric rating scale for the efficacy was BPRS. For the economic evaluation we will summarize in term of :

Response to treatment : reduce in mean score of BPRS ≥35%.

Nonresponse : reduce in mean score <35%.

2. The psychiatric rating scale for the side effects measurement was the Simpson-Angus Rating Scale[22] (Simpson Angus) for extrapyramidal symptoms.

3. Others :

Laboratory findings such as CBC (complete blood count), UA (Urinalysis), EKG (Electrocardiogram), and LFT (liver function test).

Cost Analysis

1. Direct cost

Cost will be determined for the fiscal year 1998 and expressed in Thai Baht for each intervention encounter in each alternative.

A. Direct medical cost

Cost determinations	Method of measurement
1. Antipsychotics: • Olanzapine • Haloperidol	• Cost charge from the department of pharmacy unit calculated by the dose using in one year. Mean dose of OLZ = 17 mg/day Mean dose of HAL = 25 mg/day
2. Hotel cost	• Cost from the department of finance, Ramathibodi Hospital for the psychiatric inpatient ward.
3. Labor cost **(health personnel)**	• Include psychiatrist, nurse and paramedics' salary per unit cost of patients which include inpatient treatment and out-patient follow up, also emergency treatment at emergency unit.
4. Laboratory cost	• CBC, UA, EKG, LFT • Psychological testing
5. Cost for the treatment of side effects: • EPS • Tardive dyskinesia • Neuroleptic malignant syndrome • Weight gain • Hypersomnia	• Cost include the management per one event. We estimate to be cost for each alternative by using probability of each side effect.

6. Cost for the complications of the disease:	
• Suicide attempt's treatment	• The treatment need intensive care and may be the treatment of the complication from suicide. The cost will be about two fold of normal admission
• Suicide with death	• This study would not calculate the cost because the expected life year was difficult to be converted into utility due to the condition of this disease.
7. Non response	
• Usually non-respondents need electroconvulsive therapy (ECT).	• The analysis will be based on one admission to have one course of ECT (12 times) which will perform 3 times per week. So the duration of admission is approximate 28 days.

B. Direct non medical cost

Cost determinations	Method of measurement
• Transportation	• On the cost from patient's view

2. Indirect cost

Cost determinations	Method of measurement
1. Work loss 2. Care-giver loss time and money	• Cost from patients' view. Using labour cost 162 Baht per day for the alternative treatment that cause more work loss.

3. Intangible cost

Cost determinations	Method of measurement
1. Social stigmata 2. Reaction to chronic illness	• These problems will not be analyzed in this study because the duration is one year.

Analysis

Medical Cost The total direct and indirect medical cost and were analyzed separately in each alternative by using direct medical cost from Table 1 : olanzapine, haloperidol group (Table 2 and 3).

Direct nonmedical cost There were 12 visits per year. The transportation cost of each visit was 150 Baht. The total cost for one year analysis is 1,800 Baht.

Indirect cost

Work loss: Patients on OLZ had an additional 6.8 month in a disability-free health state than HAL/5 years follow up[20]. So in one year = 1.36 month. If one day minimal income =162 Baht then HAL treatment group will have work loss=162 x 40.8 = 6609.6 per year more than OLZ.

Care-giver loss: Since whenever the patients were disabled, there must be at least one who took care of them. Therefore, we can assume the same figure as patient's work loss=6609.6 for HAL group more than OLZ.

Cost effectiveness analysis

According to the decision tree and path probability (Figure 1) the target outcome of this study is the number of patients who recover from refractory schizophrenia = healthy without complications and side effects (Outcome 1 and 9).

From Table 2 the cost of OLZ to get one healthy = 668,928.02

From Table 3 the cost of HAL to get one healthy = 1,565,337.80

Therefore, net benefit OLZ over HAL to get one case healthy in one year = 1,565,337.8-668,928.0 = 896,409.8 Baht

Incremental CE ratio

$$\textbf{OLZ vs. HAL} = \frac{\text{total cost of OLZ} - \text{total cost of HAL}}{\text{prob. of healthy (OLZ)} - \text{prob. of healthy (HAL)}}$$

$$= \frac{260657.2-78916.58}{0.389664-0.05886} = \frac{181740.62}{0.330804} = 549{,}390.63$$

Sensitivity analysis

The cost of effectiveness of each alternative may subject to change when there is some change in cost of the drugs or the efficacy of each drug. Therefore we vary the response rate of OLZ (Figure 2) and HAL (Figure 3) as well as the cost of HAL (Figure 4) to get the threshold analysis.

Discussion

The treatment of refractory schizophrenia (TRS) by using the novel atypical antipsychotic drugs has been studied in many reports. The efficacy of these drugs has been proved. However, the cost of these drugs is much more expensive than the conventional medicine. The cost effectiveness is another issue needed to be explored especially in developing countries. The guideline for treatment of TRS should be justified not only by the effectiveness but also the cost-effectiveness of each particular drug.

In this study, we compared the cost effectiveness between olanzapine (OLZ, an atypical antipsychotic drug) and haloperidol (HAL, a conventional antipsychotic drug) in the treatment of refractory schizophrenia (TRS) for one-year period.

In attempt to understand the cost effectiveness of both drugs, the economic analysis was done by using the decision tree and path probability (Figure 1). It was shown that in one-year treatment of OLZ providing more benefit over HAL by 894,409.80 Baht for one patient. In the other word, in order to get one healthy case the cost of one year treatment by OLZ is cheaper than HAL by 894,409.80 Baht.

We also used incremental CE ratio to detect the amount of additional money for the TRS patient who was currently treated by HAL and want to achieve the equal efficacy of OLZ. In the incremental CE ratio section, the calculation showed that we need 549,390.63 Baht to do so.

Even though the price of OLZ is much higher than HAL (366 Baht/10mg vs. 8.5 Baht/5mg accordingly). But the cost of complication and side effect treatment causing by HAL is much more than OLZ. When taking together with the lower response rate, the total cost of treatment by OLZ is cheaper than HAL.

This assumption was argued that the response rate of OLZ may be varied from study to study (38%-48%). We then using the sensitivity analysis to check the minimum response rate of OLZ which still can provide the advantages of the drug. As shown in Figure 2, the threshold analysis of OLZ is 21.5% by using response rate raging from 10% to 40%. This means the cost effective of OLZ will be over HAL as long as the response rate of the drug is over 21.5%. On the other way around, if HAL can provide response rate over 27.5% the cost effectiveness of HAL will be equal to OLZ (Figure 3).

Both figures answer the argument of various response rates of both drugs. If the cost of medical care was fixed these analyses have shown that the final justification should base on the final threshold of the drugs.

Since the price of HAL is varied in a wide range. The other argument is if the price of HAL becomes cheaper the cost effective of HAL may be changed from this conclusion. In order to find the minimal price of HAL that can compare to OLZ, We varied the cost of HAL from 1 Baht to 9 Baht per 5mg of HAL tablet (Figure 4). The cost of treatment consequently varied from 1,330,469 to 1,580,996 Baht per patient per year. When compare to OLZ which the cost of one patient treatment is 668,928 Baht per year, one can see that the benefit of OLZ was over HAL at any price within the range.

The result of this study favored OLZ when compare to HAL during one year treatment of TRS patient. However, we realized that the result of economic evaluation will depend on the period of time, cost estimation of drugs and medical cares, the response rate of the medications and the adverse event

rate. One who would like to apply this information need to check all estimation and wisely adapt to each particular circumstance.

Conclusion

The result of this economic evaluation suggests that the total one year cost of treatment by OLZ appears to be more effective than HAL in the treatment of TRS. This is the impact of the cost reduction of medical care for TRS patients during one year of treatment.

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