ORIGINAL PAPER

Service Utilization and Costs Associated With Switching to Risperidone from Previous Treatment with Typical Antipsychotic Agents

A Hatim, J Tan*, Mas Ayu** , H Habil**

**Dept. of Psychological Medicine, University of Malaya Medical Centre, Kuala Lumpur*
***Dept. of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur*

ABSTRACT

This study determined medical service utilization and costs associated with switching to risperidone from previous treatment with typical antipsychotic agents. 62 adult outpatients diagnosed with schizophrenia were identified from pharmacy records, with complete information regarding medical service utilization for one year before and after treatment with risperidone. Information on hospitalization, use of day care hospital, electroconvulsive therapy, emergency department, outpatient clinic services and functional parameters were collected. Cost of treatment, cost of unemployment and cost of lost productivity due to suicide were calculated. The results showed significant fewer hospitalization days, ECT sessions and emergency department visits were observed one year after switching to risperidone ($p<.05$). The total treatment costs associated with risperidone after one year was 88.8% higher than costs during the previous year of treatment with typical antipsychotic agents.

Keywords: **risperidone, schizophrenia, cost analysis**

Introduction

Schizophrenia is a serious mental illness. For majority of patients it is a lifetime condition, characterized by intermittent episodes of hospitalization due to relapse or acute symptom exacerbation(1, 2). The nature and course of the disorder impose significant social and economic burden. Relapse is costly, with hospitalization accounting for a substantial portion of healthcare expenses. Periods of acute episodes are strongly linked with unemployment. Other costs include loss of productivity among unpaid family caregivers(3). In UK, the estimated of direct cost of treatment and care of schizophrenia was about 2 billion pounds in 2004/05. The burden of indirect costs was amounting to nearly 4.7 billion pounds. The cost of lost productivity due to unemployment, absence from work and premature mortality of patients was 3.4 billion pounds.(4) In the U.S., of the estimated direct costs in 2002 of schizophrenia treatment amounted to US$22.7 billion. The indirect costs,

including losses due to unemployment were $32.4 billion.(5) The hospitalization cost associated with antipsychotic nonadherence was much higher ranging from $1392 million to $1826 million in 1995(6).

Antipsychotic pharmacotherapy continues to play an important role in reducing acute symptoms, improving functioning and preventing relapse among patients with schizophrenia(7-9). Risperidone, an atypical antipsychotic agent, has demonstrated efficacy in improving schizophrenia symptoms in both short and long-term studies(10, 11). It also has been associated with a relatively smaller risk of relapse at 1 year follow-up compared with haloperidol (1, 12-14). However, the higher acquisition cost of this drug compared to typical antipsychotic medications remains a limiting factor to its use.(15-17)

Nevertheless it has been suggested that net savings due to reductions in service utilization mediated by risperidone use may compensate for the drug's high acquisition cost(18-21). Comparison of hospitalization rates before and after initiation of risperidone in clinical trials has shown reduction in number of days hospitalized by as much as 31% – 73% (22-27). In the systematic review by Hudson and colleagues of 22 economic evaluation studies on novel antipsychotic agents(28), ten retrospective studies compared costs associated with use of risperidone versus conventional antipsychotic drugs. One study estimated costs of clinical data gathered in an experimental setting(29), while 9 studies used data gathered from patient records(29-37) . Decreased in total costs were noted in 5 studies(29, 30, 33, 36, 37), while increased in total costs were reported in 4 studies (31, 32, 34, 35). Using scores on clinical improvement as measures of effectiveness and decrease in service utilization as proxy indicators of improvement, three studies documented improved effectiveness and lower total costs associated with risperidone use(29, 30, 33). The review also noted that all of the 7 studies that used simulation models to estimate costs associated with use of atypical antipsychotic drugs, indicated cost advantages(28).

However these studies dealt primarily with patients in developed countries. Data on the economic impact of schizophrenia in developing countries was limited. Given the economic burden of schizophrenia, evaluating the costs associated with use of particular drugs was really vital. The objectives of this study was to compare medical service utilization and costs associated with switching to risperidone from previous treatment with typical antipsychotic agents among outpatients in the University of Malaya Medical Center.

Materials and Methods

Study Design and study subjects

This was a cross-sectional study of before and during risperidone treatment. The eligible study subjects were outpatients, aged 18 years and above and have a diagnosis of schizophrenia according to DSM IV criteria. All outpatients treated with oral risperidone from January 2001 to January 2005, were identified from the pharmacy records of the University of Malaya Medical Center (UMMC). The UMMC is the oldest teaching hospital and acts as a referral center for Klang Valley (Kuala Lumpur), Malaysia. It attends to approximately 24,000 psychiatric outpatients and 800 psychiatric inpatients a year.

The selection criteria was each patient must have been treated with the same typical

antipsychotic agent for at least one year. The patients later were switched to oral risperidone and maintained as outpatient for at least one year. The follow-up information for at least one year must be available from the medical records for each type of antipsychotic drug treatment.

Patients with other than Axis I diagnoses, less than one year of treatment with risperidone, taking atypical antipsychotic agents other than risperidone, or with inadequate follow-up data were excluded from the study.

Data collection

For each patient, a structured questionnaire was used to collect data for the last 12-month period prior to risperidone treatment, which was during treatment with a conventional antipsychotic drug, and for the 12-month period immediately after initiation of risperidone. All information was obtained from patients' medical record. The questionnaire was divided into three sections; demographic characteristics, medical service utilization and functional parameters during treatment.

The first section was to describe the demographic data of the study population, i.e. age, sex, race, education level and marital status. The second section was regarding medical service utilization for both treatment periods, mainly to describe the number of days hospitalized, number of electroconvulsive therapy sessions undergone, number of days spent in day care hospital, number of emergency department visits, number of scheduled clinic visits and number of unscheduled clinic visits. Number of scheduled clinic visits attended was used as an indicator of compliance to therapy. The third section was regarding functional parameters which included the use of institutional residential care, employment, showing of violent episodes requiring restraint, attempted suicides at least once and police reports against the patient at least once. The third section was used as indicators of indirect consequences of schizophrenia. Ethical approval was obtained from UMMC Ethical Committee.

Cost for treatment with typical antipsychotics and risperidone

The cost stated was the fee that needed to be paid by patients after medical service utilization. Cost of medical service utilization was calculated separately for treatment with typical antipsychotics and risperidone. It was the total cost of each type of medical services. Medical service utilization cost for hospitalization was computed by multiplying total admission day and hospitalization charges, whereas day care hospital cost was obtained by multiplying total day and day charges. Other medical service utilization was derived by multiplying the frequency of utilization and the charges of each service. Cost estimation for treatment was obtained by summation of cost of medical services and cost of medication. The hospital charges of medical service in UMMC were based on 2005 rates.

Cost estimation in lost of productivity

The functional parameters measured during treatment were employment status and attempted suicide. A further analysis was done to quantify the economic loss due to unemployment and suicide attempt using procedures described in a previous study (38, 39) The employment rate loss due to schizophrenia was calculated based on the difference between employment rates in the general population, reported by Department of Statistics, Malaysia in 2005(40) and employment rates for each antipsychotic

therapy, later multiply with monthly per capita income in 2005. Economic loss of suicide was assessed in terms of lost of employment, with the assumption that there would be lost of productivity for 6 months period in view of recovery from injury and rehabilitation. (39)The calculation of lost productivity due to suicide equal to attempt rate multiply by employment rate for each antipsychotic multiply 6-montly per capita income. The per capita income RM18,040 was used based on report by the Department of Statistics, Malaysia in year 2005(40, 41).

Statistical Analysis

Raw data obtained were coded and entered into Statistical Package for Social Sciences (SPSS) Version 15.0. For categorical variables, they were described in the form of frequencies and percentages. For continuous variables, they were summarized and described as means, standard deviations, median and range.

Differences in characteristics between groups were compared using Chi-square tests for categorical variables. 2-tailed paired t test was used for continuous variables and Wilcoxon Singed Ranks test was used for skewed distribution. Subsequently the continuous variables were recategorised and further tested by Pearson's Chi-square test. An alpha level of 0.05 was set for all analyses.

Results

Out of 400 patients that have been screened, who were initially on typical antipsychotic medication and later switched to risperidone, only 62 patients fulfilled the selection criteria. Characteristics of selected patients were shown in Table 1.

From Table 1, 56.5% were female patients; majority was between 20 to 59 years old (89%), which was also productivity age group. There was no statistically significant difference between the mean age of male and female patients. Further stratification analysis showed more female patients (30.6%) were married as compared to the males (12.9%). However, the difference was not statistically significant.

Table 1. Characteristics of patients (n = 62)

Variable	n	(%)
Gender		
Male	27	(43.5)
Female	35	(56.5)
Age group		
20-29	6	(9.7)
30-39	12	(19.4)
40-49	23	(37.1)
50-59	14	(22.6)
60-69	4	(6.5)
70 and above	3	(4.8)
Race		
Malay	6	(9.7)
Chinese	46	(74.2)
Indian	10	(16.1)
Level of Education		
No formal education	3	(4.8)
Primary	13	(21.0)
Secondary	38	(61.3)
Tertiary	8	(12.9)
Marital Status		
Single	32	(51.6)
Married	27	(43.5)
Divorced	3	(4.8)

Data on medical service utilization for typical antipsychotic medication and risperidone were shown in Table 2. Overall duration for hospital stay for risperidone was shorter and less frequent visit for multiple hospital services compared to typical antipsychotics. The number of patients hospitalized at least once declined from 17 patients during typical antipsychotic medication, to only 3 patients after the first year of treatment with risperidone. During the 1-year period of treatment with typical antipsychotic drugs, the cumulative number of days spent as in-patient was 372 days.

This would also equivalent to an average hospital stay of 6.0 + 2.4 days per patient during typical antipsychotic medication. During treatment with risperidone, hospitalization decreased to 51 days and the reduction in the number of days was 86%.

Table 2. Comparison between typical antipsychotic medication and risperidone for medical service utilization, n=62

Index of Service Utilization	Typical antipsychotic	Risperidone	p
Hospitalization(day)			<0.001*
Median	0	0	
Range	0 - 83	0 - 28	
Total	372	51	
No. of admitted patients n(%)	17 (27.4)	3 (4.8)	
Electroconvulsive therapy (ECT) sessions			0.017*
Median	0	0	
Range	0 - 8	0	
Total	45	0	
No. of patients required ECT n(%)	7 (11.3)	0	
Day care hospital(day)			0.107
Median	0	0	
Range	0 - 68	0 - 63	
Total	196	96	
No. of day care patients n (%)	7 (11.3)	3 (4.8)	
Emergency department visits			0.007*
Median	0	0	
Range	0 - 3	0 - 1	
Total	20	4	
No. of patients visited emergency department n(%)	13 (21.0)	4 (6.5)	
Outpatient clinic visits (unscheduled visit)			0.883
Median	0	0	
Range	0 - 7	0 - 5	
Total	52	53	
No. of patients visited unscheduled clinic n(%)	29 (46.8)	27 (43.5)	
Outpatient clinic visits (scheduled follow-up)			<0 .001**
Mean(SD)	3.02(1.49)	4.0(1.93)	
Median (Range)	3 (0 – 6)	4 (0 – 10)	
Total	187	248	
No. of patients visited scheduled clinic (n,%)	58 (93.5%)	58 (93.5%)	

*Statistically significantly with Wilcoxon Signed RanksTest
**Statistically significantly with Paired *t* Test

The most remarkable finding was the use of electroconvulsive therapy (ECT), as none of patients on risperidone required the therapy. The visit to emergency department has also significantly reduced with risperidone. The proportion of patients making an unscheduled outpatient clinic visit at least once was almost similar during typical antipsychotic drugs and after changing to risperidone. However, in terms of compliance with scheduled outpatient clinic visits, the data showed significantly increased attendance during treatment with risperidone.($p<0.05$)

The distribution of patients on functional parameters in Table 3 showed there was improvement in functioning with risperidone treatment compared to typical antipsychotic drugs. It also noted that during treatment with risperidone, employment increased by 80% and the violent behaviors as indicated by needed for restraint decreased by 82%. In addition, there were no reports of suicide attempts and problems with the law during risperidone treatment, compared with reports of attempted suicide among 5 patients and documented legal problems among 7 patients during treatment with typical antipsychotic agents. Economic loss related to unemployment and suicide attempts with typical antipsychotic drugs was RM 403,374 per month, while treatment with risperidone had lower cost at RM 79,677 per month.

Table 3. Distribution of patients on functional parameters, cost of unemployment and suicide during treatment with typical antipsychotic drugs and risperidone, n=62

	Typical antipsychotic		Risperidone	
	n	%	n	%
Residing in nursing home	3	42.8	4	57.2
Employed	15	35.7	27	64.3
Showing violent behavior requiring restraint	11	84.2	2	15.8
Attempted suicide at least once	5	100.0	0	0
Reported to police at least once	7	100.0	0	0
Employment rate		24.2		43.5
Suicide attempt rate		8.1		0
Cost (RM)				
Unemployment/per month		108,691		79,677
Lost productivity due to suicide/6 month		1,768,100		0

The employment rate loss due to schizophrenia = the employment rate[a] – employment rate for each antipsychotics therapy
Lost productivity due to suicide = attempt rate x employment rate for each antipsychotic therapy x 6-monthly income
[a]The employment rate for general population was 96.5% in 2005(From Department of Statistics, Malaysia)

Costs associated with each treatment were shown in Table 4. Reduction in costs due to decrease in frequency of utilization were noted for most services. After risperidone initiation, the most substantial cost reduction was observed in hospitalization expenses. There was 86.3% decreased in cost, representing a cumulative saving of RM 25,680 for the study subjects in the first year of risperidone treatment. This can be translated as an average saving in hospitalization of RM 414.19 per patient for 1 year of risperidone treatment.

Table 4. Comparison of costs during treatment with typical antipsychotic drugs and risperidone, n=62

Service Category	Hospital Charges (RM)	Typical antipsychotic		Risperidone		Difference
		Frequency	Total(RM)	Frequency	Total(RM)	
Hospitalization¶	80	372	29,760	51	4,080	-25,680
Electroconvulsive therapy	175	45	7,875	0	0	-7,875
Day care hospital ¶	35	196	6,860	96	3,360	-3,500
Emergency department services	50	20	1,000	4	200	-800
Outpatient clinic services	35	239	8,365	301	10,535	+2,170
Scheduled visit	35	187	6,545	248	8,680	
Unscheduled visit	35	52	1,820	53	1,855	
Medical service utilization cost			53,860		18,175	-35,685
Antipsychotic medication						
Typical antipsychotic	20/month	744*	14,880			
Risperidone	150/month			744*	111,600	+96,720
Total treatment cost			68,740		129,775	+61,035

*** 62 patients for 12 months treatment**
¶ the frequency for hospitalization and day care hospital counted as day

The increased number of scheduled outpatient clinic visits has shown the improvement in compliant with the follow up. Cumulative 1-year cost for outpatient clinic services increased from RM 8,365 during treatment with typical antipsychotic drugs to RM 10,535 during risperidone medication. As for the actual expenditure of antipsychotic medication, the cost for typical antipsychotic drugs and risperidone were approximately RM 5 and RM 300 per month respectively. However, patients were charged for RM 20 for typical antipsychotic drugs and RM 150 for risperidone. In one year, the charges per patient for typical antipsychotic drugs were RM 240 and RM 1,800 for risperidone.

In term of total medical service utilization cost for risperidone, there was 66.3% decreased in cost as compared to typical antipsychotic drugs. However with the higher charges on risperidone, the overall total treatment cost after switching to risperidone increased by 88.8%. The cumulative total treatment cost during treatment with typical antipsychotic drugs at RM 68,760 (RM 1,108.71 per patient), and RM 129,775 (RM 2,093.15 per patient) during treatment with risperidone.

Discussion

In many studies, atypical antipsychotic drugs had been proven to have better effectiveness compared to typical antipsychotics(42, 43). For this study, 62 outpatients with history of previous treatment with typical antipsychotic drugs, showed significantly fewer days for hospitalization, less Electroconvulsive Therapy(ECT) sessions, emergency department visits, after one year switching to risperidone. The total treatment cost was 88.8% higher after 1 year of risperidone treatment compared to treatment with typical antipsychotic drugs.

Some studies have shown a similar trend for increased costs with risperidone use (32-35), while other studies have shown contrary findings(31, 44). The reason for higher cost of risperidone for this study was due to prescribing of original drug for risperidone

and generic drug for typical antipsychotics. Although the reduction in expenses associated with these lower utilization rates could compensate for the acquisition cost of risperidone, the real treatment cost was much higher as the price of risperidone was double from what has been paid by the patients.

In this particular study however, the increased in total treatment cost with risperidone use was observed despite substantially lower service utilization costs. This suggested that antipsychotic medication expenses in developing countries account for a greater proportion of total direct costs, as opposed to developed countries. A cost-of-illness study of schizophrenia in Nigeria illustrated this point, with results showing that the main predictor of treatment expenses was the cost of the antipsychotic agents' used(39, 45).

In this study, the most significant reduction in medical service utilization cost was hospitalization. The common reason for hospitalization was relapse among schizophrenic patients, (46-49) with the reduction of hospitalization after switching to risperidone, this indicated that relapse has reduced and patients were able to have a better quality of life and be productive for their community. Several studies had also demonstrated lower risk of relapse with risperidone use compared with typical antipsychotic drugs such as haloperidol (1, 12). It has been estimated that risk of relapse in patients with schizophrenia was 3.5% per month(27). Repeated relapses might adversely affect future remission, level of disability, and heighten treatment resistance(50-53). Thus risperidone was superior in preventing relapse and providing important clinical benefits to patient and cost-savings due to fewer rehospitalization.

All functional parameters such as institutionalized residential care, employment, violent episodes, suicide attempts and police reports at least once showed improvement during treatment with risperidone. Further, when unemployment and suicide attempts during the two treatment periods were analyzed as lost productivity and valued in terms of per capita income, the economic loss during treatment with typical antipsychotic drugs were higher than costs associated with risperidone treatment. The percentage of employment with risperidone treatment in this study (64.3%) was higher than 2004 employment rates (48%) gathered by the Malaysian National Mental Health Registry among patients with schizophrenia(54). However as overall particularly in Malaysia, the social stigma attached to mental illnesses limited the employment opportunities of patients with schizophrenia(55, 56).

The findings in this study can be utilized for future implementation of National Healthcare Financing in Malaysia and strengthening the insurance coverage for patients with mental illness. This study provided information for the ability of patients and family members to pay out-of-pocket for the antipsychotic medication and utilization of medical services. Although the costing of this study for both treatments were only based on hospital charges, not the analysis of hospital costs based on direct and indirect cost, the decision on healthcare financing and insurance coverage not only aiming at cost-saving, the policy maker should also consider patients' well being and the quality of life, and beyond the calculated hospital costs. The findings on functional parameters in this study has proved that the social and economic gain were vast more with risperidone than typical antipsychotics.

There were limitations to the present study that should be taken into consideration when interpreting the results. Although this study utilized secondary data from patients' medical record, recalled bias was overcome. There would be selection bias of the participant, as only subjects with complete information for one year with typical antipsychotic and later one year with risperidone were selected. Subjects who had been treatment less than one year for both treatments might have more information regarding medical service utilization and functional parameters. The results for this group can be interpreted as cost of treatment per month. The cost of concomitant treatment should be included in the cost of medication because the information was available in the medical record.

Conclusions

The present study suggested that switching to risperidone after treatment failure or treatment intolerance of previous typical antipsychotic agents might provide clinical advantages, but not the cost of treatment. Further studies were required to investigate the relationship between the apparent clinical benefit and cost limitations of risperidone use. The findings will clarify the real impact of newer antipsychotic agents on mental health patients in developing countries.

References

1. Csernansky JG, Mahmoud R, Brenner R. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl J Med. 2002 Jan 3;346(1):16-22.

2. Altamura AC, Bobo WV, Meltzer HY. Factors affecting outcome in schizophrenia and their relevance for psychopharmacological treatment. Int Clin Psychopharmacol. 2007 Sep;22(5):249-67.

3. Knapp M. Schizophrenia costs and treatment cost-effectiveness. Acta Psychiatr Scand Suppl. 2000(407):15-8.

4. Mangalore R, Knapp M. Cost of schizophrenia in England. J Ment Health Policy Econ. 2007 Mar;10(1):23-41.

5. Wu EQ, Birnbaum HG, Shi L, Ball DE, Kessler RC, Moulis M, et al. The economic burden of schizophrenia in the United States in 2002. J Clin Psychiatry. 2005 Sep;66(9):1122-9.

6. Sun SX, Liu GG, Christensen DB, Fu AZ. Review and analysis of hospitalization costs associated with antipsychotic nonadherence in the treatment of schizophrenia in the United States. Curr Med Res Opin. 2007 Oct;23(10):2305-12.

7. Kane JM. Treatment adherence and long-term outcomes. CNS Spectr. 2007 Oct;12(10 Suppl 17):21-6.

8. Kane JM. An evidence-based strategy for remission in schizophrenia. J Clin Psychiatry. 2008;69 Suppl 3:25-30.

9. Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW. Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. J Clin Psychiatry. 2006 Mar;67(3):453-60.

10. Fakra E, Khalfa S, Da Fonseca D, Besnier N, Delaveau P, Azorin JM, et al. Effect of risperidone versus haloperidol on emotional responding in schizophrenic patients. Psychopharmacology (Berl). 2008 Oct;200(2):261-72.

11. Remillard S, Pourcher E, Cohen H. Long-term effects of risperidone versus haloperidol on verbal memory, attention, and symptomatology in schizophrenia. J Int Neuropsychol Soc. 2008 Jan;14(1):110-8.

12. Hunter RH, Joy CB, Kennedy E, Gilbody SM, Song F. Risperidone versus typical antipsychotic medication for schizophrenia. Cochrane Database Syst Rev. 2003(2):CD000440.

13. Marshall M, Rathbone J. Early intervention for psychosis. Cochrane Database Syst Rev. 2006(4):CD004718.

14. Ricciardi A, McAllister V, Dazzan P. Is early intervention in psychosis effective? Epidemiol Psichiatr Soc. 2008 Jul-Sep;17(3):227-35.

15. Edwards NC, Pesa J, Meletiche DM, Engelhart L, Thompson AK, Sherr J, et al. One-year clinical and economic consequences of oral atypical antipsychotics in the treatment of schizophrenia. Curr Med Res Opin. 2008 Dec;24(12):3341-55.

16. Obradovic M, Mrhar A, Kos M. Cost-effectiveness of antipsychotics for outpatients with chronic schizophrenia. Int J Clin Pract. 2007 Dec;61(12):1979-88.

17. Polsky D, Doshi JA, Bauer MS, Glick HA. Clinical trial-based cost-effectiveness analyses of antipsychotic use. Am J Psychiatry. 2006 Dec;163(12):2047-56.

18. Gianfrancesco F, Durkin MB, Mahmoud R, Wang RH. Use of healthcare services by patients treated with risperidone versus conventional antipsychotic agents. Pharmacoeconomics. 2002;20(6):413-27.

19. Zhao Z, Namjoshi M, Barber BL, Loosbrock DL, Tunis SL, Zhu B, et al. Economic outcomes associated with switching individuals with schizophrenia between risperidone and olanzapine: findings from a large US claims database. CNS Drugs. 2004;18(3):157-64.

20. Johnsrud M, Crismon ML, Thompson A, Grogg A. An economic comparison of risperidone and olanzapine use within an integrated managed mental health program. Adm Policy Ment Health. 2006 Mar;33(2):237-43.

21. Foster RH, Goa KL. Risperidone. A pharmacoeconomic review of its use in schizophrenia. Pharmacoeconomics. 1998 Jul;14(1):97-133.

22. Dickson RA, Dalby JT, Addington D, Williams R, McDougall GM. Hospital days in risperidone-treated patients. Can J Psychiatry. 1999 Nov;44(9):909-13.

23. Negron AE, Leiderman EA, Parkadavil M, Cienfuegos A, Javitt DC. A naturalistic outcome study of risperidone treatment among hospital patients. Psychiatr Serv. 1996 Oct;47(10):1118-20.

24. Addington DE, Jones B, Bloom D, Chouinard G, Remington G, Albright P. Reduction of hospital days in chronic schizophrenic patients treated with risperidone: a retrospective study. Clin Ther. 1993 Sep-Oct;15(5):917-26.

25. Chengappa KN, Sheth S, Brar JS, Parepally H, Marcus S, Gopalani A, et al. Risperidone use at a state hospital: a clinical audit 2 years after the first wave of risperidone prescriptions. J Clin Psychiatry. 1999 Jun;60(6):373-8.

26. Lindstrom E, Eriksson B, Hellgren A, von Knorring L, Eberhard G. Efficacy and safety of risperidone in the long-term treatment of patients with schizophrenia. Clin Ther. 1995 May-Jun;17(3):402-12.

27. Csernansky JG, Schuchart EK. Relapse and rehospitalisation rates in patients with schizophrenia: effects of second generation antipsychotics. CNS Drugs. 2002;16(7):473-84.

28. Hudson TJ, Sullivan G, Feng W, Owen RR, Thrush CR. Economic evaluations of novel antipsychotic medications: a literature review. Schizophr Res. 2003 Apr 1;60(2-3):199-218.

29. Chouinard G, Albright PS. Economic and health state utility determinations for schizophrenic patients treated with risperidone or haloperidol. J Clin Psychopharmacol. 1997 Aug;17(4):298-307.

30. Nightengale BS, Garrett L, Waugh S, Lawrence BJ, Andrus J. Economic outcomes associated with the use of risperidone in a naturalistic group practice setting. Am J Manag Care. 1998 Mar;4(3):360-6.

31. Albright PS, Livingstone S, Keegan D, et al. Reduction of healthcare resource utilization and costs following the use of risperidone for patients with schizophrenia previously treated with standard antipsycotic therapy: A retrospective analysis using the Saskatchewan Health linkable databases. Clinical Drug Investigation. 1996;11:289-99.

32. Viale G, Mechling L, Maislin G, Durkin M, Engelhart L, Lawrence BJ. Impact of risperidone on the use of mental health care resources. Psychiatr Serv. 1997 Sep;48(9):1153-9.

33. Carter C, Stevens M, Durkin M. Effects of risperidone therapy on the use of mental health care resources in Salt Lake County, Utah. Clin Ther. 1998 Mar-Apr;20(2):352-63.

34. Nightengale BS, Crumly JM, Liao J, Lawrence BJ, Jacobs EW. Economic outcomes of antipsychotic agents in a Medicaid population: traditional agents vs. risperidone. Psychopharmacol Bull. 1998;34(3):373-82.

35. Hammond CM, Pierson JF, Grande TP, Munetz MR, Wilson DR, Pathak DS. Economic evaluation of risperidone in an outpatient population. Ann Pharmacother. 1999 Nov;33(11):1160-6.

36. Schiller MJ, Shumway M, Hargreaves WA. Treatment costs and patient outcomes with use of risperidone in a public mental health setting. Psychiatr Serv. 1999 Feb;50(2):228-32.

37. Guest JF, Hart WM, Cookson RF, et al. Pharmacoeconomic evaluation of long-term treatment with risperidone for patients with chronic schizophrenia. Br J Med Econ 1996;10:59-67.

38. Foster RH, Goa KL. Olanzapine. A pharmacoeconomic review of its use in schizophrenia. Pharmacoeconomics. 1999 Jun;15(6):611-40.

39. Price N, Davey P, Birinyi-Strachan L. The cost-effectiveness of olanzapine in the treatment of schizophrenia in Malaysia. Malaysian Journal of Psychiatry. 2005;13:53-62.

40. First. Pacific-Group, Newsletter Artircle:Key Statistics, Department of Statistics Malaysia, September 2005 [cited 02012009]; Available from:

http://firstpacificgroup.com.my/applications/DocumentLibraryManager/upload/Microsoft%20Word%20-%20Key%20Statistics-DeptOfStatisticMalaysia.pdf.

41. Department. of Statistics Malaysia :Key Statistics. [cited 02012009]; Available from: http://www.statistics.gov.my/eng/index.php?option=com_content&view=category&id=38&Itemid=11.

42. Lublin H, Eberhard J, Levander S. Current therapy issues and unmet clinical needs in the treatment of schizophrenia: a review of the new generation antipsychotics. Int Clin Psychopharmacol. 2005 Jul;20(4):183-98.

43. Lyne J, Kelly BD, O'Connor WT. Schizophrenia: a review of neuropharmacology. Ir J Med Sci. 2004 Jul-Sep;173(3):155-9.

44. Finley PR, Sommer BR, Corbitt JL, Brunson GH, Lum BL. Risperidone: clinical outcome predictors and cost-effectiveness in a naturalistic setting. Psychopharmacol Bull. 1998;34(1):75-81.

45. Shah A, Jenkins R. Mental health economic studies from developing countries reviewed in the context of those from developed countries. Acta Psychiatr Scand. 2000 Feb;101(2):87-103.

46. Morken G, Widen JH, Grawe RW. Non-adherence to antipsychotic medication, relapse and rehospitalisation in recent-onset schizophrenia. BMC Psychiatry. 2008;8:32.

47. Ucok A, Polat A, Cakir S, Genc A. One year outcome in first episode schizophrenia. Predictors of relapse. Eur Arch Psychiatry Clin Neurosci. 2006 Feb;256(1):37-43.

48. de Sena EP, Santos-Jesus R, Miranda-Scippa A, Quarantini Lde C, Oliveira IR. Relapse in patients with schizophrenia: a comparison between risperidone and haloperidol. Rev Bras Psiquiatr. 2003 Oct;25(4):220-3.

49. Doering S, Muller E, Kopcke W, Pietzcker A, Gaebel W, Linden M, et al. Predictors of relapse and rehospitalization in schizophrenia and schizoaffective disorder. Schizophr Bull. 1998;24(1):87-98.

50. Turner MS, Stewart DW. Review of the evidence for the long-term efficacy of atypical antipsychotic agents in the treatment of patients with schizophrenia and related psychoses. J Psychopharmacol. 2006 Nov;20(6 Suppl):20-37.

51. Perkins DO, Gu H, Boteva K, Lieberman JA. Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. Am J Psychiatry. 2005 Oct;162(10):1785-804.

52. Leucht S, Barnes TR, Kissling W, Engel RR, Correll C, Kane JM. Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. Am J Psychiatry. 2003 Jul;160(7):1209-22.

53. Huxley NA, Rendall M, Sederer L. Psychosocial treatments in schizophrenia: a review of the past 20 years. J Nerv Ment Dis. 2000 Apr;188(4):187-201.

54. Ministry. of Health Malaysia.National Mental Health Registry's: Report 2003-2004.

55. Mubarak AR, Baba I, Chin LH, Hoe QS. Quality of life of community-based

chronic schizophrenia patients in Penang, Malaysia. Aust N Z J Psychiatry. 2003 Oct;37(5):577-85.

56. Mubarak AR. Social functioning and quality of life of patients with schizophrenia in the northern region of Malaysia.Australian e-Journal for the Advancement of Mental Health (AeJAMH),2005;4(3):1-10. [cited 5 July 2006]; Available from: www.auseinet.com/journal/vol4iss3/mubarak.pdf

Corresponding author: ***Ahmad Hatim Sulaiman, Department of Psychological Medicine, University of Malaya Medical Centre, Kuala Lumpur***

Fax number: +603 79571058

Telephone number: +6012 2310252

Email: hatim@um.edu.my