

Risperidone and Olanzapine Use at a Psychiatric Hospital: Comparison of Clinical Use and Acquisition Costs

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ABSTRACT

Objective: To determine and compare clinical use and acquisition costs for risperidone and olanzapine among hospital inpatients who received treatment with one of these drugs in a tertiary care psychiatric hospital.

Methods: In this observational study, 60 patients who had received a first prescription of risperidone or olanzapine (30 in each group) before September 30, 1997, were identified from the data files of the hospital's pharmacy. The subjects were observed for 60 days after initiation of drug treatment. If treatment was interrupted or if the patient was released from hospital before 60 days, the date of interruption or release marked the end of the observation period.

Results: For risperidone, the average daily dose prescribed at the end of the observation period was about half the dose recommended in the product monograph. Conversely, for olanzapine, the average daily dose prescribed was at least 20% higher than that specified in the monograph. At the end of the observation period, the average daily acquisition cost of olanzapine was more than twice that of risperidone ($p < 0.001$).

Conclusion: In clinical practice, the acquisition cost of olanzapine appears to be much higher than that for risperidone.

Key words: risperidone, olanzapine, acquisition cost, daily dose, schizophrenia

RÉSUMÉ

Objectif : Établir et comparer l'utilisation clinique et les coûts d'acquisition de la rispéridone et de l'olanzapine administrées à des patients ambulatoires d'un hôpital psychiatrique de soins tertiaires.

Méthodes : Au cours de cette étude d'observation, 60 patients qui avaient reçu une première ordonnance de rispéridone ou d'olanzapine (30 dans chaque groupe) avant le 30 septembre 1997, ont été identifiés à partir des données en dossiers de la pharmacie de l'hôpital. Les patients ont été observés pendant 60 jours après le début du traitement médicamenteux. Si ce dernier était interrompu ou si le patient obtenait son congé de l'hôpital avant le 60^e jour de l'étude, la date d'interruption du traitement ou de sortie marquait la fin de la période d'observation.

Résultats : La dose quotidienne moyenne de rispéridone prescrite à la fin de la période d'observation était environ la moitié de celle recommandée dans la monographie de produit. En comparaison, la dose quotidienne moyenne d'olanzapine prescrite à la fin de la période d'étude était d'au moins 20 % supérieure à celle indiquée dans la monographie. Par conséquent, à la fin de la période d'observation, le coût d'acquisition moyen quotidien de l'olanzapine était plus du double de celui de la rispéridone ($p < 0,001$).

Conclusion : En pratique clinique, le coût d'acquisition de l'olanzapine semble beaucoup plus élevé que celui de la rispéridone.

Mots clés : rispéridone, olanzapine, coût d'acquisition, dose quotidienne, schizophrénie

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INTRODUCTION

Schizophrenia is a major psychotic disorder that can be highly debilitating. The disease most commonly manifests in late adolescence to young adulthood, and the lifetime prevalence is about 1% throughout the world.¹ Schizophrenia is frequently characterized by a chronic recurrent course and, consequently, significant costs associated with health care and loss of productivity.^{1,2} In Canada, schizophrenia leads to estimated direct health care costs of \$2.3 billion and indirect support services costs of \$2 billion each year³ (all costs in Canadian dollars).

Typical antipsychotics, such as chlorpromazine and haloperidol, have revolutionized the treatment of schizophrenia and have contributed substantially to the process of deinstitutionalization in the past 30 years.⁴ However, their effectiveness has been compromised by high rates of drug-related side effects, especially extrapyramidal symptoms, which often lead to noncompliance and to drug discontinuation.^{5,6} Moreover, although typical antipsychotics can be highly effective in alleviating the positive symptoms of schizophrenia, they have a limited effect on the negative symptoms.^{7,8} As many as 20% to 30% of schizophrenic patients have inadequate or poor response to typical antipsychotics.^{9,10}

The new atypical antipsychotics (clozapine, risperidone, quetiapine, and olanzapine) exhibit pharmacological profiles that differ from those of the typical antipsychotics.^{1,7} They have superior efficacy against negative symptoms, such as social withdrawal, blunted affect, and alogia, and they have been associated with a lower risk of extrapyramidal symptoms.^{7,8}

Among the atypical antipsychotics, risperidone and olanzapine are both available as first-line treatment options for schizophrenic patients.¹¹ Although these 2 drugs differ from each other in both chemical structure and receptor affinity when compared with haloperidol, both have been shown to reduce significantly the positive and negative symptoms of schizophrenia and to improve quality of life.^{7,12}

According to the product monographs,¹³ the target daily doses are 6 mg for risperidone and 10 mg for olanzapine. At these dosages, the acquisition cost of olanzapine is only slightly higher than that of risperidone. However, it has been suggested that in clinical practice, the average prescribed daily dose of olanzapine might be higher than the target dose recommended in the monograph. For example, on the basis of a review of data derived from clinical trials and market research, Kasper¹¹ concluded that, with respect to

efficacy and tolerability, a daily dose of at least 15 mg of olanzapine appears to be required to improve symptoms, whereas the optimal daily dose of risperidone ranges between 4 and 6 mg.

The decision to treat a psychotic patient with any of the atypical antipsychotics should be based on the clinical characteristics of the illness, the therapeutic profile of the drug, and its pharmacological characteristics, but also on the real cost of the treatment. Since the acquisition costs of a drug are largely driven by the daily dose, olanzapine may have a substantially higher acquisition cost than risperidone in clinical practice. This study was undertaken to determine and compare clinical use and acquisition costs of risperidone and olanzapine among hospital inpatients.

METHODS

This observational study was performed in a tertiary care psychiatric hospital in Quebec City. The study population consisted of 60 patients, 30 who had received a first prescription for risperidone before September 30, 1997, and 30 who had received a first prescription for olanzapine before the same date. This sample size was sufficient to detect a \$3.00 difference in average daily acquisition costs at an α level of 0.05 and a power of 90%. The patients were selected from the hospital pharmacy's data files. A pharmacist reviewed the data file in reverse, first checking the prescription file for September 29, then the file for September 28, and so on, to identify patients who had received a prescription for one of the drugs. To select only those patients who were starting treatment with risperidone or olanzapine, the pharmacist also checked whether the patient had already been given the drug in the course of the current hospital stay or during a previous hospital stay. The first 30 patients with a first prescription for risperidone and the first 30 patients with a first prescription for olanzapine made up the study population.

Each patient was observed over a period of 60 days after initiation of treatment with risperidone or olanzapine. If treatment was interrupted or if the patient was discharged before completion of the 60-day period, the date of interruption or discharge marked the end of the observation period for that patient.

The pharmacist checked each patient's file to gather data on patient characteristics, illnesses, and other drugs. This review was conducted at the end of the observation period, so as not to interfere with patient care.

The following patient characteristics and clinical data were collected: date of birth, sex, date of first diagnosis of mental illness, date of hospital admission,

main diagnosis on admission, and date of discharge. With regard to the course of drug treatment, the following information was collected: names of typical and atypical antipsychotic drugs prescribed between December 1, 1987, and the end of the observation period, concentration and frequency of the daily dose of risperidone or olanzapine, start-up and end dates for each prescription for risperidone or olanzapine during the observation period, and reasons for cessation of treatment. The director of professional services in the hospital where the study took place approved the data extraction.

The acquisition costs for both risperidone and olanzapine were based on the list of medications published by the Régie de l'assurance-maladie du Québec (Quebec Health Insurance Board) in July 1997. Average daily acquisition costs were calculated on the basis of the daily dose and the unit cost of the highest concentration available. Thus, the price of a 4-mg tablet of risperidone (\$3.83) and a 10-mg tablet of olanzapine (\$6.75) were used as references. As of July 2001, these costs remained the same.

The study variables for the 2 treatment groups were compared by means of chi-square tests for categorical variables and *t*-tests for continuous variables, with an *a priori* significance level of 0.05. Fisher exact tests were used for categorical variables when the expected value in a cell was equal to or less than 5. No statistical test was used to compare the average daily doses of risperidone and olanzapine, since the 2 drugs do not

have the same potency. All analyses were performed using the SAS statistical software package, version 6.12 (SAS Institute, Carey, NC).

RESULTS

The characteristics of the patients in the 2 groups were similar, except for average age and prior use of the other atypical antipsychotic (Table 1). Risperidone-treated patients were older than olanzapine-treated patients ($p = 0.008$), and prior use of olanzapine by patients in the risperidone group was less frequent than prior use of risperidone by patients in the olanzapine group ($p = 0.01$).

Seventeen subjects (57%) treated with risperidone and 12 (40%) treated with olanzapine were still receiving the study drug after 60 days in hospital ($p = 0.20$) (Table 2). Of the 25 subjects discharged from hospital within 60 days, 11 were on risperidone and 14 on olanzapine ($p = 0.43$). Two risperidone treatments and 4 olanzapine treatments were discontinued after less than 60 days. One risperidone and 2 olanzapine treatments were stopped because of an apparent lack of effectiveness, and the others were stopped because of side effects.

For each study drug, the average daily doses prescribed by the 60th day of treatment and at discharge were comparable (2.85 and 3.23 mg respectively for risperidone and 12.85 and 12.14 mg respectively for olanzapine). At the end of the observation period, the average daily acquisition cost of olanzapine was significantly higher than that of risperidone ($p < 0.001$).

Table 1. Characteristics of Study Subjects at Initiation of Treatment

Characteristic	Risperidone Group (n = 30)	Olanzapine Group (n = 30)	p
Sex (no. and %)			
Women	12 (40)	13 (43)	
Men	18 (60)	17 (57)	0.80
Average age ± SD (years)	55.1 ± 16.0	44.1 ± 15.2	0.008
Primary diagnosis (no. and %)			
Schizophrenia	15 (50)	10 (33)	0.19
Bipolar affective disorder	5 (17)	5 (17)	NC
Major depression with psychotic features	2 (7)	2 (7)	NC
Schizoaffective disorder	0	4 (13)	NC
Other	8 (27)	9 (30)	NC
Average duration of mental illness ± SD (years)	19.8 ± 15.4	14.5 ± 13.0	0.16
Prior use of the other atypical antipsychotic (no. and %)			
Yes	4 (13)	13 (43)	0.01
No	26 (87)	17 (57)	0.41
Average no. ± SD of antipsychotics used in 10 years preceding treatment with study drugs	3.10 ± 2.51	3.60 ± 1.87	0.41
	3.10 ± 2.51	3.60 ± 1.87	0.41

SD = standard deviation, NC = not computed because of small sample size.



Table 2. Treatment Outcomes and Acquisition Costs*

Outcome or Cost	Risperidone Group (n = 30)	Olanzapine Group (n = 30)	p
Still receiving study drug in hospital after 60-day period			
No. (and %) of subjects	17 (57)	12 (40)	0.20
Average daily dose at 60th day ± SD (mg)	2.85 ± 2.58	12.85 ± 3.99	
Average daily acquisition cost at 60th day ± SD (\$)	2.73 ± 2.48	8.44 ± 2.69	<0.001
Discharged with study drug within 60-day period			
No. (and %) of subjects	11 (37)	14 (47)	0.43
Average daily dose at discharge ± SD (mg)	3.23 ± 1.40	12.14 ± 15.2	
Average daily acquisition cost at discharge ± SD (\$)	3.09 ± 1.34	8.20 ± 3.68	<0.001
Treatment with study drug stopped within 60-day period			
No. (and %) of subjects	2 (7)	4 (13)	NC
Average daily dose at discontinuation ± SD (mg)	4.25 ± 2.47	10 ± 5.77	
Average daily acquisition cost at discontinuation ± SD (\$)	4.07 ± 2.37	6.75 ± 3.90	NC

SD = standard deviation, NC = not computed because of small sample size.

*The acquisition costs in July 2001 were the same as those in 1997, the time of the study.

The average number ± standard deviation of typical antipsychotics used concurrently with the study drugs during the observation period was 1.27 ± 0.45 for risperidone-treated subjects and 1.55 ± 0.67 for olanzapine-treated subjects ($p = 0.11$).

DISCUSSION

For both risperidone and olanzapine, there was a significant discrepancy between doses prescribed and doses specified in the product monographs. The average daily dose of risperidone prescribed was about half the specified dose, whereas the average daily dose of olanzapine prescribed was at least 20% higher than the specified dose. The average daily acquisition cost of olanzapine at the end of the observation period was more than 2.5 times that of risperidone. The gap between the average prescribed dosages and those specified in the monographs, combined with the unit cost of each of the drugs, explains the large difference in acquisition costs.

These findings on doses and costs agree with the results of a previous study performed in a British Columbia hospital.¹⁴ The latter study also compared the use of risperidone and olanzapine in groups of 30 patients. The average daily dose of olanzapine prescribed was 19.8 mg, twice the dosage recommended in the product monograph. The average daily dose of risperidone prescribed (5.8 mg) conformed with the dosage specified in the monograph. These average daily doses are higher than those observed in the present study. This difference may be explained by the higher average age of patients in the present study (by about

15 years) or by differences in professional practices between the 2 provinces.

Lower dosages of risperidone are recommended for elderly patients.¹⁵ In the present study, the average age of the risperidone-treated patients was 55 years, and 10 were aged 65 or older. However, even for the patients who were less than 65 years of age, the average daily dose of risperidone (3.4 ± 1.7 mg) was less than the dose specified in the monograph. This suggests that, in the hospital where these data were gathered, the usual daily dose of risperidone is about 3.0 mg, regardless of the patient's age.

No rating scale of psychotic symptoms was used to check the comparability of the groups in terms of severity of illness. Therefore, it is impossible to exclude the possibility that the higher acquisition cost of olanzapine was due, at least in part, to greater severity of illness in the group treated with this drug. However, the various markers of severity of the episode of mental illness (duration of illness, number of antipsychotics received before current treatment, length of observation period, and number of antipsychotics used concurrently with the drug in the study) were similar in the 2 groups (Table 1).

There was no statistically significant difference between the 2 groups in the proportion of subjects discharged with the study medication within 60 days ($p = 0.43$). In contrast, in a previous study carried out in British Columbia, a greater proportion of patients treated with risperidone than patients treated with olanzapine left the hospital during the 120-day observation period.¹⁴ This difference between the 2 studies may relate



to the study subjects: the present study included only patients who were starting treatment with risperidone or olanzapine, whereas Procyslyn and Zerjav¹⁴ did not take into account duration of exposure to treatment before study entry. By including in their sample subjects for whom a variable period had elapsed between the start of treatment and the start of observation, these researchers may have introduced a selection bias. Indeed, patients who had been receiving risperidone or olanzapine for some time when they were admitted to the study might have had a greater probability of a positive outcome than patients who were just starting a new treatment.

Prior use of olanzapine by patients in the risperidone group was less frequent than prior use of risperidone by patients in the olanzapine group. This may be because risperidone was launched on the market in 1993, some 3 years before olanzapine became available. Therefore, the probability of observing a switch from risperidone to olanzapine was higher. Further research is required to clarify this finding.

Two subjects stopped taking risperidone and 4 stopped taking olanzapine before the conclusion of the 60-day observation period. The reasons for cessation of treatment, as recorded in the patient's file, did not permit the presumption of a difference in either efficacy or innocuousness between the 2 drugs. In fact, the number of treatment cessations was small and the information available is such that there can be no reliable comparison of the 2 groups as to severity of illness, response to treatment, or incidence of undesirable side effects.

No published data permit the conclusion that olanzapine displays therapeutic benefits that justify its much higher acquisition costs. Tran and others¹⁵ carried out a double-blind randomized clinical trial to compare the efficacy and adverse effect profile of risperidone and olanzapine. They observed a higher incidence of extrapyramidal reactions ($p = 0.008$ for spontaneously reported extrapyramidal adverse events) and a weaker improvement in negative symptomatology ($p = 0.02$) with risperidone. However, the overall response rate, as measured by the PANSS (positive and negative syndrome scale) total score, was similar for the 2 treatment groups ($p = 0.413$).

The study by Tran and others¹⁵ was the subject of much criticism.^{11,16,17} The majority of the critics emphasized that the study methodology was biased against risperidone. First, Tran and others¹⁵ analyzed the results by way of a one-tailed statistical test, which increased the probability of asserting a significant

difference in favour of olanzapine.^{16,17} Use of one-tailed statistical tests is inappropriate unless there exists a theoretical basis suggesting that one treatment is superior to another, which was not the case with olanzapine and risperidone. The one-tailed test also made it impossible to identify the clinical parameters by which risperidone might have been superior to olanzapine.¹⁷ Second, the rapid titration of the doses and the attainment of a mean modal dose of 7.2 mg/day may have contributed to the high incidence of extrapyramidal reactions associated with risperidone.^{11,16} Indeed, daily doses of more than 6 mg/day are routinely not recommended since they are linked to a much higher incidence of extrapyramidal reactions without a substantial increase in efficacy.¹¹ The average daily dose of 7.2 mg obtained in the study by Tran and others¹⁵ does not represent the average dosage used in the clinical setting (i.e., around 3 mg per day in the present study). The results reported by Tran and others¹⁵ may not then be generalizable to current practice.

Since this study was performed in a tertiary care setting, caution should be exercised in generalizing its results to other institutions or the entire population. In particular, further studies are needed in the ambulatory setting.

This study was conducted to determine the prescribed daily doses of risperidone and olanzapine given to hospital inpatients at a tertiary care psychiatric hospital. The average acquisition cost of the drugs were also compared. On average, the prescribed daily dose of risperidone corresponded to half the dosage specified in the monograph, whereas for olanzapine, the prescribed dosage was at least 20% higher than the specified dosage. These differences affected treatment acquisition costs, which were more than 2.5 times higher for olanzapine-treated patients than for risperidone-treated patients. Nonetheless, the decision to treat a psychotic patient with risperidone or olanzapine should not be based on acquisition cost alone; equally important are the clinical characteristics of the illness, the therapeutic profile of the drug, and its pharmacological characteristics. Consequently, a head-to-head comparison of both the cost and the effectiveness of these drugs is warranted.

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