A Swiss retrospective naturalistic outcome study comparing risperidone and olanzapine in the treatment of schizophrenic inpatients[1, 2]

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Summary

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Atypical anti-psychotics such as clozapine, risperidone and more recently olanzapine have become the cornerstone of the treatment of schizophrenia. These drugs have superior efficacy and tolerability and a better compliance than conventional anti-psychotics, translating into lower relapse and re-hospitalisation rates.

The RODOS program (Risperidone Olanzapine Drugs Outcome studies in Schizophrenia) was designed to provide outcomes data for risperidone and olanzapine used in a naturalistic clinical setting. This international retrospective study was conducted on 1901 inpatients. The present paper compares the drug-usage pattern and the costs and outcomes associated with the treatment of schizophrenia or schizo-affective disorders with either risperidone or olanzapine in Switzerland.

Retrospective chart reviews were carried out in five Swiss hospitals, for inpatients for whom either risperidone or olanzapine was the drug of first intention for long-term treatment. Patients selected were aged ≤65 years and diagnosed with schizophrenia or schizo-affective disorder. Socio-demographic data and clinical information were collected in patients' files, as well as hospitalisation information and usage pattern of all drugs used during the stay in hospital. Treatment efficacy was recorded, as well as time to efficacy, time to discharge, treatment discontinuation and spontaneously reported side effects. Treatment was rated as "effective" or "ineffective" according to the patient's file as noted by the treating physician. Drug prices (including concomitant medication) were calculated and expressed in local currency at the level of the hospital pharmacy purchasing price.

The total population comprised 312 patients, 154 receiving risperidone and 158 receiving olanzapine. The two treatment groups did not have significant differences regarding sociodemographic characteristics, history of schizophrenia and use of previous anti-psychotics. The risperidone and olanzapine groups were comparable in terms of number of days before efficacy was established, proportion of patients with effective treatment (83 vs 85%, p = 0.67), number of patients with symptom improvement, discontinuation rate and time to discharge (median 31 vs 41 days, p = 0.32). Mean dosage at the end of treatment for those patients who were discharged was 3.8 mg for risperidone and 14.9 mg for olanzapine.

The average daily cost of the study medication was significantly higher for olanzapine than for risperidone (geometric mean: 11.33 vs 4.15 CHF, p <0.0001). The total cost of the treatment drug was also significantly higher for olanzapine compared to risperidone (geometric mean: 289.0 vs 92.0 CHF, respectively, p <0.0001). During the treatment period, 47 patients (31%) treated with risperidone and 49 patients (31%) treated with olanzapine experienced adverse events.

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These results show that both treatments have comparable efficacy and short-term side-effect profile, with an almost three times lower cost for risperidone. This is true in all comparisons: all inpatients drugs or study medication only, total population or responding patients, whole hospitalisation or treatment period only. Thus, assuming the same effectiveness for risperidone and olanzapine, but higher costs for the latter drug, the cost-effectiveness ratio of risperidone is to be considered more favourable.

For a single patient, the choice of an anti-psychotic treatment relies on various parameters, including previous patient's and clinician's experiences. Compared to the total costs of a schizophrenic inpatient, the drug costs may be considered relatively small. This dramatically changes when the patient is discharged. For example, on the basis of the average daily dose of the study medication at the time of discharge found in this study, the average cost per patient per year amounts CHF 2130.– for risperidone, and CHF 6630.– for olanzapine. When considering a patient population, costs can guide a strategic decision, as any waste of resources may lower the overall clinical output achieved on the whole population.

Keywords: schizophrenia; outcome; cost-effectiveness; risperidone; olanzapine

Introduction

Schizophrenia is a psychiatric disorder affecting 1% of the general population with treatment costs accounting for approximately 2.5% of total health care expenditures, mainly due to hospitalisations. Atypical anti-psychotics such as clozapine, risperidone and more recently olanzapine have become the cornerstone of treatment. These drugs have superior efficacy and tolerability and a better compliance than conventional anti-psychotics, translating into lower relapse and rehospitalisation rates [1–3]. Current evidence suggests that the rehospitalisation rates of risperidone and olanzapine are similar [3].

Due to their higher acquisition costs, the pharmacoeconomics of anti-psychotic agents have received a great deal of attention. Until recently, not much was known about the differential cost effectiveness of atypical anti-psychotics. A comparison between risperidone 6 mg/day and olanzapine 10 mg/day based on a model developed by Palmer et al. suggested a superior cost-effectiveness for olanzapine [4]. However, this result has been questioned because the dosages used in the model were not reflecting actual clinical practice and because the results of the model proved to be very sensitive to changes in this assumption [5–8]. The authors themselves admit that when olanzapine 15 mg is compared to risperidone 6 mg, then risperidone is superior. Lecompte et al. come to this conclusion in a comparable study [9]. Thus, in order to better characterise the pharmacoeconomics of risperidone and olanzapine, there clearly was a need for outcome data collected in real life.

The results of clinical studies often do not give precise information about the outcomes to be expected in real life. The patients enrolled in such studies are often not representative of the real patient population, and the intervention differs from normal clinical practice. For this reason, from the societal perspective, retrospective outcome studies may be necessary to better describe reality. Of course, these studies also have their limitations. For example, interesting data may be missing because they are not recorded in clinical practice. Furthermore, the risk of bias must also be adequately addressed with the corresponding design and the statistical analysis plan.

The RODOS program (Risperidone Olanzapine Drugs Outcome studies in Schizophrenia) was designed to provide outcomes data for risperidone and olanzapine used in a naturalistic clinical setting [10, 11]. In this international retrospective study conducted on 1901 inpatients, the average daily dose used was 5.3 mg for risperidone and 14.5 mg for olanzapine.

Due to differences in the organisation of the national health care systems, the results of cost-effectiveness studies are not necessarily transposable across borders. Our study used the RODOS methodology and was aimed at analysing the situation in Switzerland. Two additional issues were addressed in this study, i.e. symptomatology (symptoms present upon admission and improvement) and tolerability.

Methods

Detailed methodology has previously been described [10]. Briefly: data were collected in five Swiss centres from patients who had been discharged from hospital or who had been in hospital 120 days, and for whom risperidone or olanzapine was the drug of first choice for long-term pharmacological treatment after admission. Patients would stay in the same group even after a subsequent change of anti-psychotic medication.

Patients were admitted for hospitalisation between December 1993 and May 2000. Patients selected for inclusion in the study met the follow-

ing criteria: (i) aged ≤65 years; (ii) diagnosed with schizophrenia or schizo-affective disorder according to ICD-10 [12]; (iii) discharged from hospital; (iv) if not discharged, at least 120 follow-up days in hospital. In order to eliminate selection bias and introduce an element of randomisation into the patient-selection process, the most recent admissions in which either risperidone or olanzapine was the drug of first choice for long-term treatment were included in reverse chronological order. A sample size of 33 per treatment group was the target for each centre. No patient was included more than one time. Study design was uniform across all participating centres, with the same protocol, data collection form and data collection procedures being used throughout.

Sociodemographic data (age, gender) and clinical information (age at diagnosis, number of previous hospitalisations, medication history, diagnosis upon admission, symptoms present upon admission and improvement) were collected in patients' files, as well as hospitalisation information and usage pattern of all drugs used during the stay in hospital.

A number of clinical outcomes were recorded, including treatment efficacy, time to efficacy, time to discharge, treatment discontinuation and spontaneously reported side effects. Treatment was rated as "effective" or "ineffective" according to the patient's file as noted by the treating physician.

Drug prices (including concomitant medication) were calculated on the basis of the 1998 national market data from the market research institute IMS-Health and expressed in local currency at the level of the hospital pharmacy purchasing price (olanzapine 0.8345 CHF/mg, risperidone 1.202 CHF/mg).

The statistical analysis plan was predefined and was the same for all the participating centres. All tests were two-sided with an alpha level of 0.05. Statistical calculations were carried out using SAS Software for Windows (version 6.12). Descriptive methods were used to analyse the dosage parameters without any statistical comparison between treatments. The Pearson chi-square test was used to compare the proportion of patients in the treatment groups that achieved specific outcomes, and the time to event parameters were assessed using survival analysis methods to account for the censored data. Quantitative parameters, such as number of days, were compared using non-parametric Mann-Whitney test due to their non-normal distribution. The Kaplan-Meier product-limit estimate of the survival function was calculated for analysis of time to efficacy and time to discharge and the risperidone and olanzapine survival functions compared using a non-parametric test (log-rank test).

A predefined analysis plan was conducted to correct for potential baseline differences between the treatment groups using covariance analysis. Age at onset, age at admission, gender, number of previous hospitalisations and use of anti-psychotics during the previous year were included as covariates in the analysis.

Key outcome parameters were assessed including percentage of patients discharged before or at day 120, length of hospitalisation, number of patients with effective treatment, time to efficacy, number of discontinuations and average daily dose. Numeric scores were adjusted using analysis of covariance on $\log_{10}$-transformed data. The adjusted means are therefore effectively adjusted geometric means and are, due to the correction for skewness, lower than the unadjusted means. Comparisons of risperidone and olanzapine in terms of percentage outcomes, which are dichotomous in nature, were reported as odds ratios and adjusted through logistic regression.

Results

Patient population

Sociodemographic and clinical data are listed in table 1. The total population comprised 312 patients, 154 receiving risperidone and 158 receiving olanzapine. The two treatment groups did not have significant differences regarding sociodemographic characteristics, history of schizophrenia and use of previous anti-psychotics. 247 patients were responders (119 risperidone and 128 olanzapine, table 2).

Treatment efficacy and dosage

The risperidone and olanzapine groups were comparable in terms of time between admission and start of treatment (7.3 vs 8.6 days, p = 0.48), number of days before efficacy was established (13.7 vs 17.2, p = 0.17), proportion of patients with effective treatment (83 vs 85%, p = 0.67), number of patients with symptom improvement (all p values >0.23), discontinuation rate (15 vs 13%, p = 0.50), switch rate (10 vs 9%, p = 0.72), duration of studied treatment (32.0 vs 39.3 days, p = 0.14), total hospitalisation duration (46.3 vs 51.5, p = 0.39), time to discharge (median 31 vs 41 days, p = 0.32) and proportion of patient discharged before 120 days (87 vs 86%, p = 0.94). The time to

Table 1 Demography and history of schizophrenia.

parameter	risperidone (n = 154)	olanzapine (n = 158)	p*
age at onset of first symptoms (years)[a]	27.8 ± 9.9	26.4 ± 9.0	0.15
age at admission (years)	35.5 ± 11.4	36.2 ± 12.2	0.90
gender n (%) males	92 (60%)	93 (59%)	0.98
diagnosis			0.56
catatonic schizophrenia	4 (3%)	2 (1%)	
disorganised schizophrenia	9 (6%)	7 (4%)	
paranoid schizophrenia	77 (50%)	96 (61%)	
undifferentiated schizophrenia	16 (10%)	11 (7%)	
residual schizophrenia	1 (1%)	2 (1%)	
schizo-affective	28 (18%)	26 (16%)	
other diagnosis	19 (12%)	14 (9%)	
previous hospitalisation	122 (79%)	129 (82%)	0.67
number of previous hospitalisations[b]			
0	32 (21%)	27 (17%)	0.09
1–5	79 (51%)	75 (48%)	
6–10	31 (20%)	27 (17%)	
11–20	9 (6%)	17 (11%)	
>20	3 (2%)	10 (6%)	
use of anti-psychotics during the previous year[c]	111 (89%)	124 (94%)	0.15
number of patients who discontinued previous anti-psychotics[d]			
for any reason	81 (73%)	77 (62%)	0.08
for lack of efficacy	7 (6%)	14 (11%)	0.23
for side effects	25 (23%)	26 (21%)	0.85
for other reason(s)	57 (51%)	50 (40%)	0.08

Values are numbers of patients (%) except for age: mean ± SD (minimum, median, maximum).
* = probability associated with the hypothesis of no difference between the two groups (Anova for age, Standard Cochran-Mantel-Haenszel test for gender, previous hospitalisations, use of anti-psychotics, diagnosis and Cochran-Mantel-Haenszel on the standardised mid-ranks for the number of previous hospitalisation and number of anti-psychotics);
[a] = age at onset of first symptoms, n = 157 for olanzapine;
[b] = percentages are calculated using the patients with previous hospitalisations (n = 154 and 156 patients for risperidone and olanzapine, respectively);
[c] = percentages are calculated using the number of patients with available history of medications as denominator (n = 125 and 132 patients for risperidone and olanzapine, respectively);
[d] = percentages are calculated using the patients who took previous anti-psychotics (n = 111 and 124 patients for risperidone and olanzapine, respectively).

Table 2 Participating centres and patients numbers.

centre	hospital / clinic	total		responders	
		RIS	OLA	RIS	OLA
1	Département universitaire de psychiatrie adulte, Lausanne	33	31	29	26
2	Département de psychiatrie, HUG, Genève	34	32	32	30
3	Psychiatrische Universitätsklinik, Zürich	25	32	19	27
4	Psychiatriezentrum Münsingen, Münsingen	33	33	17	26
5	Kantonale Psychiatrische Klinik Waldhaus, Chur	29	30	22	19
total		**154**	**158**	**119**	**128**
		312		**247**	

RIS = risperidone; OLA = olanzapine.

discharge curves of risperidone and olanzapine were statistically different for the responder population (median 25 vs 36 days, p = 0.04).

Dosages of risperidone and olanzapine used are listed in table 3. The average daily dose was 3.7 ± 1.4 mg risperidone and 14.5 ± 5.0 mg olanzapine. Mean dosage at the end of treatment for those patients who were discharged was 3.8 mg for risperidone and 14.9 mg for olanzapine.

Concomitant medication

The risperidone and the olanzapine groups were comparable in terms of the proportion of patients taking other neuroleptics (whole hospitalisation period: 69 vs 70%; actual treatment period: 54 vs 64%; at discharge: 32 vs 36%). The two treatment groups did not significantly differ regarding any of the other relevant concomitant drug utilisation parameters.

Tolerability

During the treatment period, 47 patients (31%) treated with risperidone and 49 patients (31%) treated with olanzapine experienced adverse events (p = 0.92). The most frequent adverse events were disorders of the central and peripheral nervous systems like hyperkinesia, extrapyramidal disorders and dyskinesia (risperidone: 18 patients; olanzapine: 25 patients) followed by "body as a whole – general disorders" like fatigue and rigors (risperidone: 13 patients; olanzapine: 16 patients).

Table 3 Dosage characteristics, descriptive statistics.

parameter	risperidone (n = 154)	olanzapine (n = 158)
starting dose (mg)	2.4 ± 1.7 (0.5; 2; 8)	11.1 ± 5.6 (5; 10; 30)
average daily dose (mg)	3.7 ± 1.4 (1.0; 3.7; 7.1)	14.5 ± 5.0 (5.0; 14.5; 30.0)
maximum daily dose (mg)	4.3 ± 1.6 (1; 4.0; 10)	16.5 ± 5.7 (5; 17.5; 35)
modal daily dose (mg)	3.9 ± 1.5 (1; 4; 8)	15.0 ± 5.8 (5; 15; 30)
dose (mg) at the end of treatment period[a]	3.8 ± 1.6 (1; 4; 10)	14.7 ± 5.5 (2.5; 15; 30)
dose (mg) at the end of treatment for patient who discharged[b]	3.8 ± 1.5 (1; 4; 8)	14.9 ± 5.5 (2.5; 15; 30)

Dose parameters were calculated over the period from start of treatment up to discharge, treatment discontinuation or day 120; values are means ± SD (minimum; median; maximum).
[a] = dose at day 120, discharge or treatment discontinuation, whatever occurred first;
[b] = only discharged patients were considered (n = 134 and 136 for risperidone and olanzapine, respectively).

Table 4 Cost (CHF) of drug utilisation, descriptive statistics.

parameter	risperidone (n = 154)	olanzapine (n = 158)
duration of intake of the studied medication (days)	32.0 ± 29.7 (1; 23; 120)	39.2 ± 33.4 (1; 28; 120)
total cost of treatment drug	150.6 ± 171.3 (2.4; 98.6; 947.2)	488.5 ± 485.4 (8.4; 310.9; 2653.7)
daily cost of treatment drug	4.46 ± 1.67 (1.08; 4.46; 8.52)	12.08 ± 4.19 (4.17; 12.10; 25.04)
daily cost of other neuroleptics	0.43 ± 1.13 (0.00; 0.01; 6.90)	0.47 ± 0.89 (0.00; 0.13; 7.15)
daily cost of other relevant concomitant medications	0.75 ± 1.19 (0.00; 0.28; 7.69)	0.84 ± 1.37 (0.00; 0.31; 7.94)
total cost of *all* inpatient medications	191.5 ± 236.1 (2.6; 117.6; 1618.4)	535.4 ± 518.0 (8.4; 348.5; 2726.0)
daily cost of *all* inpatient medications	5.64 ± 2.20 (1.50; 5.19; 13.49)	13.39 ± 4.64 (4.65; 12.78; 29.61)

Values are means ± SD (minimum; median; maximum).

Costs of inpatient drugs

Cost of the study treatment (risperidone or olanzapine), other neuroleptics and other relevant concomitant medications is summarised in table 4. Total cost and daily cost of the treatment drug as well as total cost and daily cost of all inpatient drugs were significantly higher in the olanzapine group than in the risperidone group. This holds true after adjustment for covariates (geometric mean: total cost of treatment drug: 289.0 vs 92.0 CHF, $p < 0.0001$; daily cost of treatment drug: 11.33 vs 4.15 CHF, $p < 0.0001$; total cost of all inpatient drugs: 321.7 vs 116.4 CHF, $p < 0.0001$; daily cost of all inpatient drugs: 12.61 vs 5.25 CHF, $p < 0.0001$).

Discussion

The results of the present pooled, multi-centre study carried out in 312 inpatients with schizophrenia or schizo-affective disorders from five centres in Switzerland showed that the proportion of patients for whom efficacy could be established (as rated by the treating physician) with the studied treatment was similar with both treatments, i.e. risperidone: 83% and olanzapine: 85% respectively. This can be compared with two prospective trials. The first study from Conley and Mahmoud [8] showed a comparable efficacy of these two medications overall and in the domains of negative symptoms, hostility and disorganised thoughts, whereas positive symptoms and anxiety/depression were better improved by risperidone. The second study from Tran et al. [13] also showed a similar efficacy overall but better efficacy of olanzapine in negative symptoms and a better response rate. However, this trial has been faulted for major design and analytic issues, in particular the unusual dosing schedules (7.2 mg/day risperidone and 17.2 mg/day olanzapine) [6, 7]. It is obviously difficult to compare these prospective studies to the present work, based on data collected retrospectively. However, it may be noted that the doses of treatments given in this naturalistic setting, i.e. 3.7 ± 1.4 mg/day for risperidone and 14.5 ± 5.0 mg/day for olanzapine, do not differ much from those given in the study of Conley and Mahmoud [8] cited above (4.8 mg/day risperidone and 12.4 mg/day olanzapine), as does the efficacy observed.

Overall, the total and the daily drug costs were significantly higher for olanzapine than for risperidone. This is true in all comparisons: all inpatient drugs or study medication only, total population or responding patients, whole hospitalisation or treatment period only. The average daily cost of all inpatient medications taken during the treatment was 2.4-fold higher with olanzapine than with risperidone (geometric mean: 12.61 vs 5.25 CHF, $p < 0.0001$). Kasper and colleagues found statistically significant differences between the risperidone and olanzapine groups in the mean daily doses of study medication used (5.3 vs 14.5 mg), the total and daily cost of all inpatient medications (USD 159.9 vs 297.5 and 4.6 vs 7.7 respectively), the daily cost of study medication (USD 3.7 vs 6.5), the percentage of patients for which the study medication was considered to be effective (84 vs 79%), the time to efficacy (13.6 vs 18.6 days) and the length of hospital stay (43.6 vs 47.4 days) [10, 11]. Our study basically confirms these results in the special context of Switzerland. With a much smaller set of data, statistical significant differences were found in the mean daily doses of risperidone and olanzapine used (3.7 vs 14.5 mg), the total and daily cost of all inpatient medications (CHF 92.0 vs 289.0 and 5.25 vs 12.61 respectively) and the daily cost of study medication (CHF 4.15 vs 11.33). There were no statistical significant differences in safety parameters analysed. Thus, assuming the same effectiveness for risperidone and olanzapine, but higher costs for the latter drug, the cost-effectiveness ratio of risperidone is to be considered more favourable.

Compared to the total costs of a schizophrenic inpatient, the drug costs may be considered relatively small. This dramatically changes when the patient is discharged. For example, on the basis of the average daily dose of the study medication at the time of discharge found in this study, the average cost per patient per year amounts CHF 2130.– for risperidone and CHF 6630.– for olanzapine. For those patients, for whom no difference in efficacy and tolerability can be expected, this suggests the use of risperidone as drug of first choice for long-term treatment, with the possibility of a later switch if medically indicated, rather than the opposite strategy. The investment of the cost difference in additional treatment measures like psychosocial care may help increase the global health status of the whole patient population.

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