Risperidone Compared With Olanzapine in a Naturalistic Clinical Study: A Cost Analysis

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Background: Risperidone and olanzapine are thought to have broadly similar clinical effects. This study was designed as a cost analysis study comparing costs and basic clinical outcomes of treatment with risperidone or olanzapine in a naturalistic setting.

Method: The U.K. Risperidone Olanzapine Drug Outcomes Studies in Schizophrenia (RODOS-UK) program consisted of a retrospective review of medical notes and prescription charts for 501 patients with schizophrenia or schizoaffective disorder who had been admitted to the hospital for the treatment of psychosis. The main outcome measure was cost of inpatient drug treatment. Clinical outcomes (clinician-assessed and -documented effectiveness, time to discharge) were also evaluated. Data were collected and verified between June and September 2000.

Results: Clinical outcomes were similar for risperidone and olanzapine. Clinician-assessed effectiveness was similar for both treatments (78% risperidone, 74% olanzapine; $p = .39$), but mean time to documented onset of effectiveness was significantly shorter for those treated with risperidone versus olanzapine (17.6 vs. 22.4 days; $p = .01$). Risperidone-treated patients stayed a mean of 9 fewer days in the hospital compared with olanzapine-treated patients (49 vs. 58 days; $p = .007$). The possibility that these observed differences were a result of different baseline characteristics could not be entirely discounted. Mean ± SD doses of risperidone and olanzapine were 5.5 ± 2.4 mg/day and 14.1 ± 4.7 mg/day, respectively. The mean daily cost of all inpatient drugs was significantly higher for olanzapine than for risperidone (£5.63 vs. £3.92; $p < .0001$). Mean total costs of all inpatient drugs were significantly higher for olanzapine than for risperidone (£164 vs. £96; $p < .0001$), which partly reflected the longer mean treatment duration for olanzapine compared with risperidone (44 vs. 37 days). Concomitant antipsychotic use was similar for both groups (66% risperidone, 67% olanzapine). The number of patients documented as experiencing adverse events was not different between groups (22% risperidone, 19% olanzapine; $p = .32$).

Conclusion: Risperidone and olanzapine produced broadly comparable clinical outcome in this cohort of hospitalized patients, but the use of risperidone was associated with significantly lower drug treatment costs.

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Atypical antipsychotics for the treatment of schizophrenia are said to have a number of advantages over older, conventional neuroleptics. These advantages include improved or equivalent efficacy[1,2] and reduced incidence of distressing side effects such as extrapyramidal symptoms (EPS).[3,4] Of the atypicals available, risperidone and olanzapine are the most widely prescribed. Both agents appear to be better tolerated than a typical comparator, and superior efficacy has also been suggested in some studies.[5–12] Recent meta-analyses of all published studies support these earlier findings in single trials.[13,14]

Improved compliance may result from better efficacy and reduced side effect burden, and, indeed, lower rates of relapse and hospital readmission have been associated with risperidone and olanzapine when compared with conventional neuroleptics.[15–19] A recent long-term trial of 365 patients with DSM-IV–defined schizophrenia and schizoaffective disorder strongly suggested the superiority of risperidone over haloperidol in terms of rates of relapse and reduction of symptoms.[18]

Although both risperidone and olanzapine are well tolerated and efficacious, there is some debate over relative efficacy. There are few randomized, double-blind studies comparing the 2 treatments. In one such study,[20] patients (N = 377) showed significant improvements in total Positive and Negative Syndrome Scale scores for both treatment groups, although risperidone (mean dose = 4.8 mg/day) appeared to be significantly superior to olanzapine (mean dose = 12.4 mg/day) for the control of positive symptoms, anxiety, and depression. Extrapyramidal side effects did not significantly differ between treatments. However, another study[21] (N = 399) found olanzapine (17.2 ± 3.6 mg/day) to have an advantage in overall

response, maintenance of response, and incidence of adverse events over risperidone at relatively high doses (7.2 ± 2.7 mg/day).

The treatment of schizophrenia is costly, estimated to be approximately £2.6 billion per year in England alone.[22] Although conventional drugs have a lower purchase cost than the atypical antipsychotics, improved clinical outcome with the newer agents has been suggested to reduce the number and duration of patient hospitalizations, number of rehospitalizations, medical staff time, and use of other mental health services.[15,23,24] Cost savings associated with reductions in relapse rates and hospitalizations have been demonstrated for both risperidone and olanzapine.[11,25,26] There are few cost-effectiveness studies directly comparing risperidone and olanzapine, but in 2 recent chart reviews, risperidone appeared to be more cost-effective than olanzapine for the treatment of schizophrenia.[27,28]

The Risperidone Olanzapine Drug Outcomes Studies in Schizophrenia (RODOS) program is a series of linked single-center studies involving countries throughout Europe and Australasia. It compares the drug use patterns, outcomes, and costs associated with risperidone and olanzapine treatment in a large naturalistic population. The pooled results of 61 hospitals from 9 countries (including 2 hospitals from the United Kingdom) have been recently reported, suggesting risperidone to be similar or superior to olanzapine in effectiveness while being associated with lower drug costs.[29,30] The present study reports the results from 11 centers in the United Kingdom that participated in the separate RODOS-UK program, but that were not included in the wider study, as data were collected at a later date.

METHOD

Study Design and Patients

This U.K. study followed the same method as that of the international RODOS program.[29,30] The RODOS-UK program consisted of a series of retrospective prescription chart and medical note reviews comparing risperidone and olanzapine among 501 hospitalized patients from 11 centers (psychiatric units within a hospital environment). 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 patients per treatment group was calculated to be required for worthwhile statistical analysis of individual centers. Centers recruited from 20 to 66 patients each (mean ± SD = 45.5 ± 18.1).

Patients not older than 65 years were eligible for entry into the study. The main criteria for inclusion were that patients were admitted for the treatment of psychosis, diagnosed with schizophrenia or schizoaffective disorder, received either risperidone or olanzapine as first-line treatment, and were discharged from the hospital or, if not discharged, had at least 120 follow-up days in the hospital.

Data were collected retrospectively from the medical records of patients by an independent, trained team of pharmacists and nurses and covered the period from admission to discharge up to a maximum of 120 days of hospitalization. Two periods of interest were considered: period 1, the total period from admission to day 120 or discharge, whichever occurred first, and period 2, the period of treatment from the start of study treatment to day 120, discharge, or treatment discontinuation, whichever occurred first. The primary period of interest was period 2, which enabled assessment of study treatment costs.

The total, or intent-to-treat, population was analyzed. The total population consisted of all patients treated with either risperidone or olanzapine. Responders were defined as those in whom the treatment was documented as being effective and not discontinued, except if treatment was no longer deemed necessary.

The study design was uniform across all participating centers, with the same protocol, data collection form, and data collection procedures used throughout. Results from each participating center were entered into an integrated database by the independent team of assessors. The results reported here comprise pooled data from all U.K. centers collected and verified between June and September 2000.

Outcome Measures

The primary outcome measure was the mean daily cost of inpatient drug use, including antipsychotics and other relevant concomitant medications.

Secondary outcome measures included mean daily dose and cost of risperidone and olanzapine; treatment efficacy, rated as effective (a documented positive statement of treatment effectiveness in the patient's medical records, later validated by subsequent discharge) or ineffective (the absence of a positive statement of effectiveness or documented statement of ineffectiveness) by the attending clinician, who assessed symptoms and any improvement using clinical judgment; time to first documented effectiveness, defined as above; length of hospitalization; treatment discontinuations; and spontaneously reported side effects (i.e., documented side effects reported by the patient without prompting from the clinician).

Statistical Analysis

In a previous Canadian study, mean daily drug costs were CA$4.69 for risperidone and CA$11.52 for olanzapine ($\delta$ = CA$7.23, SD = CA$3.40).[27] Assuming a power of 90% and a significance level of .05, a sample size of 5 patients per group is required to show a statistically significant difference in cost between the 2 treatments. On a more conservative basis, assuming daily costs of 115 Luxembourg francs (LUF) for risperidone and 150 LUF for olanzapine, a sample size of 33 patients per group is re-

quired to confirm lower daily drug treatment costs for patients taking risperidone.[31] A sample size of 33 patients per treatment group was therefore the target for each center.

Statistical calculations were carried out using SAS Software for Windows (Version 6.12, SAS Institute, Inc., Cary, N.C.). Dosage parameters were analyzed using descriptive methods (mean, standard deviation, median, minimum, and maximum), with no statistical comparison between treatments. Costs of risperidone and olanzapine were analyzed by descriptive statistics but also compared using analysis of variance with stratification for center on the log-transformed data (log-normal distribution fitted the data better than normal distribution). Mean cost was expressed as the geometric mean adjusted for center (95% confidence intervals).

The proportion of patients in the treatment groups that achieved specific outcomes was compared using the Cochran-Mantel-Haenszel test, controlling for center. The Cochran-Mantel-Haenszel test on standardized mid-ranks (extension of the Mann-Whitney rank test) was used to compare illness duration, and the numbers of previous hospitalizations, previous antipsychotics, and days before efficacy were established. Time-to-event parameters were assessed using survival analysis methods to account for the censored data (patients for whom efficacy was not achieved or who were not discharged). 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 were compared using nonparametric tests with stratification for center (generalized Wilcoxon test and log-rank test).

Correction for Baseline Differences Between Treatment Groups

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 hospitalizations, and use of antipsychotics during the previous year were included as covariates in the analysis. 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

Overall, 11 centers agreed to participate in RODOS-UK, and all returned data. In these centers, the prescription charts and clinical notes of 501 patients were reviewed, of which 2 were excluded because the details of their dose of study medication were unavailable. Hence, 499 patients made up the study population, 240 receiving risperidone and 259 receiving olanzapine (total or intent-to-treat population).

Table 1. Demographic and Clinical Characteristics of Patients With Schizophrenia or Schizoaffective Disorder

Parameter	Risperidone (N = 240)	Olanzapine (N = 259)	p Value[a]
Age at onset of first symptoms, mean (SD), y[b]	26.3 (8.7)	26.0 (7.6)	.63
Age at admission, mean (SD), y	36.7 (11.8)	35.8 (11.6)	.47
Gender, N (%)			.98
Male	163 (68)	178 (69)	
Female	77 (32)	81 (31)	
Diagnosis, N (%)			.30
Catatonic schizophrenia	2 (1)	1 (0)	
Disorganized schizophrenia	2 (1)	4 (2)	
Paranoid schizophrenia	114 (48)	136 (53)	
Undifferentiated schizophrenia	58 (24)	67 (26)	
Residual schizophrenia	20 (8)	11 (4)	
Schizoaffective disease	32 (13)	33 (13)	
Schizophrenia not otherwise specified	12 (5)	7 (3)	
No. of previous hospitalizations, N (%)[c]			.28
0	64 (30)	63 (28)	
1–5	124 (57)	124 (54)	
6–10	24 (11)	30 (13)	
11–20	3 (1)	12 (5)	
> 20	1 (0)	0 (0)	
Use of antipsychotics during the previous year, N (%)[d]	176 (90)	195 (89)	.83
No. of previous antipsychotics discontinued, N (%)[d]			.04
0	75 (38)	77 (35)	
1	91 (46)	88 (40)	
2	24 (12)	36 (16)	
3	5 (3)	11 (5)	
4	0 (0)	7 (3)	
5	0 (0)	1 (0)	
6	1 (1)	0 (0)	

[a]Analysis of variance used for age; standard Cochran-Mantel-Haenszel test used for gender, use of antipsychotics, and diagnosis; and Cochran-Mantel-Haenszel on the standardized mid-ranks used for the number of previous hospitalizations.
[b]Risperidone N = 217, olanzapine N = 246.
[c]Risperidone N = 216, olanzapine N = 229.
[d]Risperidone N = 196, olanzapine N = 220.

The treatment groups had similar baseline demographic characteristics (Table 1). There was also no statistically significant difference between the treatment groups in the history of hospitalizations or antipsychotic treatment received during the previous year (a medication history was available for a similar number of patients receiving risperidone and olanzapine [82% and 85%, respectively]). The number of antipsychotics previously discontinued by patients was significantly different between the treatment groups (p = .04) (Table 1). Clozapine, which is sometimes used as an indicator of antipsychotic treatment resistance, had been taken by similar numbers of patients in each group before the start of study treatment (risperidone, N = 10, 5.1%; olanzapine, N = 13,

Table 2. Treatment Efficacy and Discontinuation in Patients With Schizophrenia or Schizoaffective Disorder

Parameter	Risperidone (N = 240)	Olanzapine (N = 259)	p Value[a]
Patients with effective treatment, N (%)[b]	182 (78)	184 (74)	.39
No. of days before efficacy was established, mean (SD)[c]	17.6 (17.9)	22.4 (20.1)	.01
Patients who discontinued, N (%)	47 (20)	53 (20)	.87
Treatment no longer deemed necessary, N	2	2	
Lack of efficacy, N	18	31	
Side effects, N	9	6	
Other reason, N	18	14	

[a]Cochran-Mantel-Haenszel test.
[b]Efficacy assessed for risperidone N = 234, olanzapine N = 247.
[c]Statistics calculated on patients in whom efficacy was established, i.e., risperidone N = 174, olanzapine N = 177.

Table 3. Adverse Events[a] in Patients With Schizophrenia or Schizoaffective Disorder

	Risperidone (N = 240)		Olanzapine (N = 259)		
Adverse Event Category	N	%	N	%	p Value
Any category[b]	53	22	48	19	NS
Body as a whole	5	2	6	2	NS
Central and peripheral nervous system	34	14	25	10	NS
Psychiatric	20	8	19	7	NS
Gastrointestinal	11	5	9	4	NS
Metabolic and nutritional	0	0	3	1	NS
Heart rate and rhythm	0	0	1	0	NS
Others	11	5	5	2	NS

[a]Classified according to World Health Organization Adverse Reaction Terminology.[32]
[b]Patients may have experienced more than 1 category of adverse event.

5.9%). There were 173 patients (72%) and 175 patients (68%) defined as responders in the risperidone and olanzapine groups, respectively.

Treatment Effectiveness

Treatment was defined as "effective" in 78% (N = 182) of patients treated with risperidone and 74% (N = 184) of those treated with olanzapine (p = .39) (Table 2). The mean ± SD time to documented onset of effectiveness was significantly (p = .01) shorter for risperidone (17.6 ± 17.9 days) than for olanzapine (22.4 ± 20.1 days). The proportion of patients who discontinued treatment in each group was similar (risperidone, N = 47, 20% vs. olanzapine, N = 53, 20%). The main reason for treatment discontinuation in each group was lack of effectiveness (risperidone, N = 18, 8%; olanzapine, N = 31, 12%).

Tolerability

Treatment with either risperidone or olanzapine was well tolerated, and no significant difference was observed in the numbers of patients documented as experiencing an adverse event (risperidone, N = 53, 22%; olanzapine, N = 48, 19%; p = .32) (Table 3). The most commonly documented category of adverse events was those affecting the central and peripheral nervous systems (risperidone, N = 34, 14%; olanzapine, N = 25, 10%).

The most frequently documented adverse event in both treatment groups was somnolence (risperidone, N = 17, 7.1%; olanzapine, N = 15, 5.8%). Extrapyramidal disorder was documented in 2.5% (N = 6) of risperidone patients and 3.5% (N = 9) of olanzapine patients. Metabolic and nutritional disorders were documented in the olanzapine group (N = 3, 1.2%), but not in patients treated with risperidone (N = 0), with weight gain accounting for all of these cases. Similarly, 1 patient (0.4%) in the olanzapine group had a documented heart rate and rhythm disorder, specified as QT interval prolongation, though no such events were reported in the risperidone group.

Table 4. Dosage Characteristics for Risperidone and Olanzapine in Patients With Schizophrenia or Schizoaffective Disorder

	Risperidone (mg) (N = 240)		Olanzapine (mg) (N = 259)	
Dose	Mean	SD	Mean	SD
Starting dose	3.9	2.5	11.8	5.3
Daily dose	5.5	2.4	14.1	4.7
Maximum daily dose	6.4	2.7	15.9	5.7
Modal daily dose	5.8	2.6	14.5	5.2
Final dose[a]	5.7	2.7	14.4	5.3
Discharge dose[b]	5.6	2.6	14.0	5.0

[a]Dose at day 120, discharge, or treatment discontinuation, whichever occurred first.
[b]Discharged patients only (risperidone N = 207, olanzapine N = 208).

Drug Use

Daily dose. The mean ± SD starting dose of risperidone was 3.9 ± 2.5 mg/day, and the mean daily dose throughout the treatment period was 5.5 ± 2.4 mg/day (Table 4). The mean olanzapine starting dose was 11.8 ± 5.3 mg/day, rising to a mean daily dose of 14.1 ± 4.7 mg/day (Table 4). The dosing patterns in the 2 treatment groups were consistent across the participating centers.

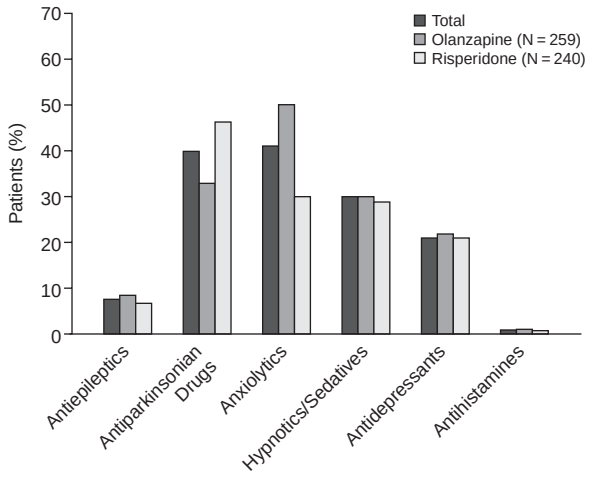
Concomitant medications. The number of patients receiving concomitant neuroleptic medication during the treatment period was similar for both groups (risperidone, N = 159, 66%; olanzapine, N = 173, 67%; p = .93). At discharge, the number of patients receiving concomitant neuroleptic comedication was lower in both treatment groups (risperidone, N = 81, 39%; olanzapine, N = 73, 35%; p = .31).

Concomitant antipsychotic medication included both typical and (rarely) atypical antipsychotics. During the total hospital stay (period 1) and during the treatment period only (period 2), the number of other antipsychotics taken by patients ranged from 1 to 11 and 1 to 6, respectively (Table 5). The most frequently taken "add-on" anti-

Table 5. Number of Patients With Respect to the Number of Other Neuroleptics Taken During the Study Period (period 1) and During the Treatment Period (period 2)

No. of Other Neuroleptics	Period 1				Period 2				End Period 2				At Discharge			
	Risperidone		Olanzapine		Risperidone		Olanzapine		Risperidone		Olanzapine		Risperidone		Olanzapine	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
0	68	28.3	67	25.9	81	33.8	86	33.2	147	61.3	175	67.6	126	60.9	135	64.9
1	94	39.2	95	36.7	97	40.4	91	35.1	80	33.3	70	27.0	70	33.8	66	31.7
2	42	17.5	57	22.0	44	18.3	56	21.6	13	5.4	13	5.0	11	5.3	7	3.4
3	28	11.7	23	8.9	14	5.8	22	8.5	0	0.0	1	0.4	0	0.0	0	0.0
4	4	1.7	10	3.9	2	0.8	2	0.8	0	0.0	0	0.0	0	0.0	0	0.0
5	2	0.8	5	1.9	2	0.8	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0
6	1	0.4	2	0.8	0	0.0	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0
11	1	0.4	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
All	240	100.0	259	100.0	240	100.0	259	100.0	240	100.0	259	100.0	207	100.0	208	100.0

Figure 1. Use of Other Concomitant Medications by Anatomical and Therapeutic Classification Group



psychotics (at any time during the study) were droperidol (23% of risperidone patients, 29% of olanzapine patients), chlorpromazine (16%, 20%), haloperidol (12%, 15%), and thioridazine (11%, 12%). All other drugs were received as add-on therapy by fewer than 10% of subjects. Fewer than 5% of subjects received any atypical as add-on therapy.

The proportion of patients receiving other relevant concomitant medication during the treatment period in the risperidone group was 79% (N = 190) and in the olanzapine group was 75% (N = 193) (p = .09). At discharge, these values were 51% (N = 105) for risperidone and 45% (N = 94) for olanzapine (p = .15). Comparing the use of other concomitant medications by anatomical and therapeutic classification group shows that for both groups anxiolytics and antiparkinsonian medications contribute the largest relative share (Figure 1).

Cost of Inpatient Drug Use

An analysis was conducted to correct for the baseline differences between groups using covariance analysis. The size and statistical significance of the differences between risperidone and olanzapine for mean daily cost of treatment drug and all inpatient drugs were similar for the unadjusted and adjusted results. Unadjusted (Table 6) and adjusted (Tables 6 and 7) results expressed as geometric means and 95% confidence intervals are described. All costs are in pounds sterling (£) (£1 equaled 1.61 Euros and US$1.44 at the time of the study).

The mean total cost of all inpatient drugs was significantly ($p < .0001$) higher for olanzapine (£163.80) than for risperidone (£96.20) (Table 6). The mean daily cost of all inpatient medication was also significantly greater for olanzapine compared with risperidone (£5.63 vs. £3.92; $p < .0001$) (Figure 2). The majority of this daily cost can be attributed to the treatment drugs, with olanzapine being significantly more costly than risperidone (£4.94 vs. £3.32; $p < .0001$) (Figure 3, Table 6).

The mean daily cost of other neuroleptics was identical in the risperidone and olanzapine groups (£0.03) (see Table 6). Similarly, the mean daily cost of other medications was also comparable for risperidone and olanzapine (£0.04 vs. £0.03, respectively; p = .14) (see Table 6).

Generally, similar cost patterns were observed in all individual U.K. study centers (see Figures 2 and 3) with the exception of center 14, where the daily cost of all medications was similar between the 2 treatments.

Hospitalization

Most patients treated with risperidone (N = 207, 86%) or olanzapine (N = 208, 80%) were discharged on or before day 120. The mean ± SD length of study treatment duration was significantly less for risperidone (37.2 ± 33.6 days) than olanzapine (44.2 ± 35.0 days) (p = .019). The mean ± SD total duration of stay was significantly less for the risperidone group (48.9 ± 39.1 days) compared with the olanzapine group (57.5 ± 39.8 days) (p = .007). Risperidone was associated with a significantly shorter time to discharge compared with olanzapine **(**$p \leq .007$**)** (Figure 4). The median time to discharge was shorter for risperidone than for olanzapine at 36 days and 47 days, respectively.

Table 6. Cost of Drug Use (£)

Type of Cost	Risperidone (N = 240) Geometric Mean (95% CI)	Olanzapine (N = 259) Geometric Mean (95% CI)	p Value[a]
Total cost of treatment drug	81.6 (69.7 to 95.4)	143.6 (123.7 to 166.8)	< .0001
Daily cost of treatment drug	3.32 (3.14 to 3.52)	4.94 (4.68 to 5.21)	< .0001
Daily cost of other neuroleptics	0.03 (0.02 to 0.04)	0.03 (0.02 to 0.04)	.99
Daily cost of other relevant comedications	0.04 (0.03 to 0.06)	0.03 (0.02 to 0.04)	.14
Total cost of all inpatient drugs	96.2 (82.4 to 112.3)	163.8 (141.3 to 190.0)	< .0001
Daily cost of all inpatient drugs	3.92 (3.70 to 4.16)	5.63 (5.32 to 5.96)	< .0001

[a]Probability associated with the hypothesis of no difference between the 2 treatment groups (analysis of variance with stratification for center on log-transformed data).

Table 7. Mean (95% CI) Costs (£) Adjusted for Differences Between Groups

	Unadjusted			Adjusted[a]		
Parameter	Risperidone	Olanzapine	p Value	Risperidone	Olanzapine	p Value
Daily cost of all inpatient drugs, period 1	3.55 (3.30 to 3.83)	4.58 (4.26 to 4.91)	< .0001	3.39 (3.09 to 3.72)	4.42 (4.04 to 4.83)	< .0001
Daily cost of all inpatient drugs, period 2	3.92 (3.70 to 4.16)	5.63 (5.32 to 5.96)	< .0001	3.82 (3.55 to 4.10)	5.53 (5.16 to 5.93)	< .0001

[a]Mean costs adjusted using analysis of covariance on $\log_{10}$-transformed data. Adjusted means are effectively geometric adjusted means and by definition lower than unadjusted means.

Figure 2. Mean (95% CI) Daily Costs of All Inpatient Medications for Intent-to-Treat Patients by Center and Pooled (period 2)

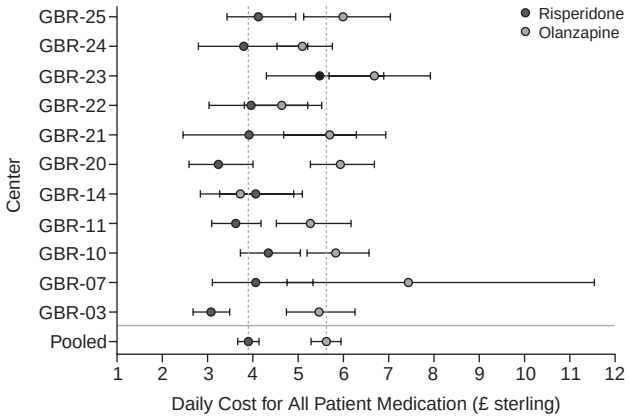
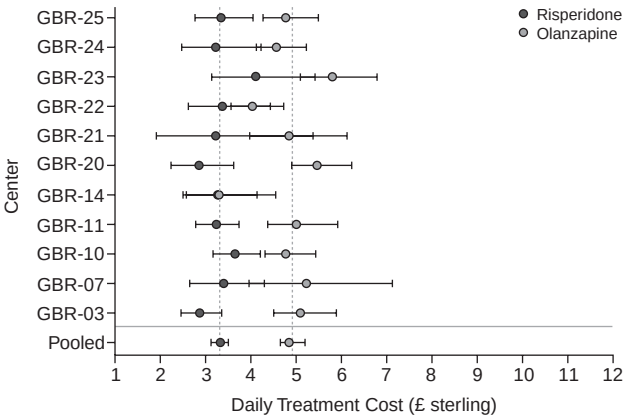


Figure 3. Mean (95% CI) Daily Costs of Study Treatment for Intent-to-Treat Patients by Center and Pooled (period 2)



Correction for Baseline Differences Between Treatment Groups

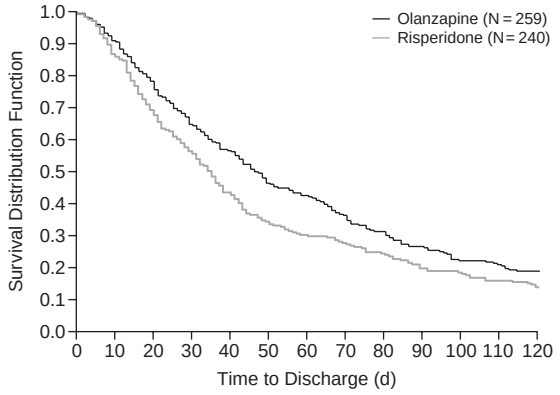
After correction for the baseline differences, there was no relevant change in the magnitude or significance of any outcome parameter (Table 7). For example, the difference between risperidone and olanzapine for the mean daily cost of all inpatient drugs (period 2) before and after adjustment was £1.71.

DISCUSSION

The RODOS program is the first large-scale international retrospective study comparing drug use patterns, basic outcomes, and costs associated with the treatment of schizophrenia with risperidone and olanzapine in a naturalistic setting.[29,30] The present RODOS study in 11 centers in the United Kingdom supports the findings of the international data: risperidone and olanzapine showed similar effectiveness, but treatment costs were significantly lower in patients prescribed risperidone.

In this study, the time taken for effectiveness to be noted in clinical records was significantly shorter for risperidone than for olanzapine. Additionally, the length of hospital stay was significantly shorter for patients treated with risperidone than olanzapine. While these findings reflect the findings from 2 Canadian retrospective studies reporting rates of hospital admission and discharge,[27,28] other factors may explain the apparent differences in outcome. For example, an important limitation of this study was that treatment effectiveness was determined by the

Figure 4. Time Distribution Function of Time to Discharge of Intent-to-Treat Patients[a]



[a]Observations censored at day 120 or at completion, whichever occurred first.

clinician and relied on clinicians' accurate and prompt recording of their opinion in clinical notes. This is a broad method of measuring treatment efficacy and may account for the apparent differences between treatments, but it does reflect everyday practice in a clinical setting. Time to discharge is clearly a more robust indicator of perceived efficacy, but this measure is also influenced by other factors somewhat divorced from drug effectiveness, such as availability of supported accommodation. Moreover, both documented effectiveness and time to discharge were likely to have been influenced by baseline characteristics of patients in the 2 treatment groups.

Coprescribing of antipsychotics was common in both groups of patients, but in both groups treatment moved toward either risperidone or olanzapine monotherapy during the study. It is notable that the reported use of concomitant medications here may represent an overestimation of the true picture. A conservative approach was adopted to measure comedication use such that any overlap in medication use, even by 1 day, and during switching of treatments with overlapping titration periods, was included. Nevertheless, the high rates of antipsychotic polypharmacy, although reflecting normal U.K. practice,[33] make difficult a true assessment of the effectiveness of risperidone or olanzapine when used alone. Similar rates of coprescribing do, perhaps, suggest similar efficacy for the 2 atypicals evaluated.

Analysis of the use of concomitant medications indicated that more patients on olanzapine treatment than on risperidone treatment were given anxiolytics, whereas the converse was true for antiparkinsonian drugs, perhaps reflecting their differing receptor affinity profiles.[34] These different rates are difficult to interpret because of coprescribing of antipsychotics. Also, nearly two thirds of patients had received other antipsychotics in the year before the study period. However, a factor possibly adding to the use of antiparkinsonian drugs was that nearly a third of patients were taking risperidone doses greater than the recommended 4 to 6 mg/day, where efficacy is maximized but the risk of side effects, such as EPS, begins to increase.[35] At clinically relevant doses of risperidone (2–6 mg/day) and olanzapine (5–20 mg/day), there appears to be no difference between the treatments in the reported number of patients with EPS.[20] Four patients received over 20 mg/day of olanzapine.

The doses used in this study emphasize another possible confounding factor. It is possible that, because the dose of risperidone is effectively limited by emergent EPS, risperidone may be used for relatively easier-to-treat patients than is olanzapine, a drug for which dose escalation is not usually problematic.

The cost of daily treatment for these patients was significantly higher for olanzapine than for risperidone (total mean daily costs of £5.63 vs. £3.92), while the cost of additional medications, including other neuroleptics, was insignificant. In practice, selection of risperidone over olanzapine might therefore provide substantial cost savings without deleterious effects on outcome. Significantly lower acquisition costs for risperidone over olanzapine and overall patient management costs have been demonstrated in similar studies.[27,28]

The results of this study should be set against other findings. The cost-effectiveness of risperidone and olanzapine have previously been compared by modeling effectiveness and costs from short-term trial data and combining these with epidemiologic data and expert panel judgment.[36,37] The earlier model suggested that olanzapine was more cost-effective than risperidone at doses of olanzapine, 10 mg/day, and risperidone, 6 mg/day. However, the reverse was predicted in a sensitivity subanalysis at more clinically comparable doses (olanzapine, 15 mg/day; risperidone, 6 mg/day).[36] The model of Lecomte et al.[37] showed that risperidone was less costly than olanzapine at the more realistic doses of 4 to 6 mg/day and 15 mg/day, respectively. The optimum dose for risperidone is 4 to 6 mg/day, and doses below 6 mg/day are associated with improved symptom control and hospital discharge and reduced risk of extrapyramidal disorders.[38–40] The optimum dose of olanzapine is suggested to be 15 mg/day.[9,10] These doses are in accordance with current U.S. and international guidelines.[41,42]

Although higher than for conventional neuroleptics, drug acquisition costs of atypical antipsychotics are low when compared with the overall cost of schizophrenia treatment. Much of this cost is due to hospitalization.[22] This study and the international RODOS study show that olanzapine is associated with a significantly longer period of hospital stay (olanzapine, 58 days; risperidone, 49 days).[29] This finding suggests that risperidone may impart further cost savings from hospitalization when

compared with olanzapine. However, given that RODOS studies are not randomized, these findings may also reflect subtle differences in baseline characteristics (particularly number of previous antipsychotics discontinued)—olanzapine may be more likely to be used for the more difficult-to-treat patients (those requiring sedation, for example).

Nonetheless, naturalistic studies should be considered as complementary to randomized controlled trials, as they reflect everyday clinical practice and avoid protocol treatment bias. This study reflects the treatment patterns of 11 centers distributed throughout the United Kingdom. Love et al.,[40] in their naturalistic study, demonstrated that as the use of risperidone has increased, the mean ± SD dose has declined from 6.4 ± 3.6 mg/day in 1994 to 5.1 ± 2.9 mg/day in 1996.

As already noted, the current study was not randomized. However, a range of baseline characteristics were recorded to discover, if possible, any fundamental differences in patients prescribed olanzapine or risperidone. There were some differences at baseline, specifically, in the number of previous antipsychotics discontinued by patients. When compared with risperidone-treated patients, more of the olanzapine group had discontinued a greater number of previous medications, which may imply that this group was more treatment resistant and so may account for the apparent differences seen in treatment efficacy. However, subsequent correction for baseline differences between treatment groups revealed no changes in the size of the differences of the study findings. It is, however, also important to note that patients may have differed importantly in other respects; for example, we did not compare prior outpatient treatment or use of facilities, or comorbidities such as substance abuse.

The results of RODOS-UK support those of the full international RODOS program. Risperidone was tentatively associated with a faster documented speed of onset and shorter hospital stays than olanzapine. Both agents were of similar effectiveness and were well tolerated. The mean doses of risperidone (5.5 ± 2.4 mg/day) and olanzapine (14.1 ± 4.7 mg/day) support the currently recommended doses, and the reduction of concomitant medications indicates a shift to their use as monotherapy. The current data indicate that the cost of olanzapine treatment for hospitalized patients with schizophrenia or schizoaffective disorder is nearly twice that of risperidone. These higher costs were not associated with any apparent clinical benefit. This study therefore suggests that risperidone may offer a real and meaningful advantage over olanzapine as drug therapy for inpatients with schizophrenia and demonstrates that, in theory, more patients can be treated with risperidone than olanzapine within the confines of a fixed budget for atypical antipsychotic drugs. The potential savings outlined may well be achievable within a hospital setting and may represent an opportunity for clinicians, pharmacists, and hospital managers to reapportion and rationalize funding without adversely affecting patient care. The findings of this study do, however, relate only to the short-term treatment of hospitalized patients. Further study is required to establish the relative value of these drugs in terms of longer-term costs, effectiveness, or cost-effectiveness in other settings.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), droperidol (Inapsine and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal), thioridazine (Mellaril and others).

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