Service Use and Costs of Treating Schizophrenia With Atypical Antipsychotics

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Background: The high acquisition cost of the atypical antipsychotics has prompted their closer clinical and economic evaluation. This study aims to examine the financial implications of using atypical antipsychotics in a defined catchment area sample of patients with schizophrenia.

Method: Service costs over a 10-month period were compared between groups of patients fulfilling DSM-IV criteria for schizophrenia who were taking different atypical antipsychotic agents.

Results: All patients studied were taking clozapine (N = 31), risperidone (N = 19), or olanzapine (N = 41). Clozapine was used in more chronic patients, while risperidone and olanzapine were prescribed in both chronic and recently diagnosed cases. After background group differences were controlled for, patients on risperidone treatment incurred the lowest costs. The monthly costs for the clozapine and olanzapine groups were higher than for risperidone by US $246 and US $566, respectively.

Conclusion: Clozapine was reserved for more severe forms of schizophrenia, but its cost impact was relatively low. Risperidone, as prescribed in ordinary practice, may be more cost-effective than olanzapine.

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The introduction of atypical antipsychotics has been heralded as a major advancement in the treatment of schizophrenia. Their higher acquisition cost has prompted close evaluation of the cost-effectiveness of atypical agents compared with conventional neuroleptics.[1] Although this issue is still under debate, the increasing rate of use of atypical antipsychotics[2,3] suggests that cost-effectiveness comparisons between different atypical antipsychotics are also urgently required.

Long-term prospective randomized cost-effectiveness trials are regarded as the gold standard, although the feasibility of such studies and the extent to which their findings apply to naturalistic clinical settings are questionable.[4] Two published randomized comparisons of risperidone and olanzapine suggested that in both acute and longer-term treatment these 2 drugs are broadly similar in their clinical efficacy and cost-effectiveness.[5] However, 2 studies based on ordinary clinical data suggest an advantage of risperidone over olanzapine. Procyshyn and Zerjav[6] collected information about medication costs and clinical outcomes from a nonrandom sample of patients with schizophrenia prescribed either olanzapine or risperidone upon hospital admission. Clinical response rates were higher and drug acquisition costs were lower for the risperidone treatment group. Rabinowitz et al.[7] collected dosage information on olanzapine and risperidone from the Israeli national registry, a database of all patients prescribed atypical antipsychotics. The national guidelines restrict the use of atypicals to patients with a diagnosis of schizophrenia who have not responded to at least 2 typical neuroleptics or who are intolerant to their side effects. In this data set, medication costs were much lower for the risperidone compared with the olanzapine treatment group. Clinical decision modeling is another approach to estimating the comparative cost-effectiveness of atypicals. Two published studies have used this method, one finding in favor of olanzapine over risperidone[8] while the other did not report significant differences between the 2 drugs.[9] The number of studies comparing the clinical effectiveness of new atypical antipsychotics with that of clozapine is at present too small to allow for any firm conclusions to be drawn.[10]

The aim of this study was to examine the cost implications of using atypical antipsychotics in a catchment-area–defined treatment sample of patients with schizophrenia. Although not without its shortcomings, this approach may give a clearer picture of the economic impact of atypicals in routine clinical care.

METHOD

Subjects

We performed a point prevalence survey (census day was July 31, 1998) of a psychiatric service within the

South London and Maudsley National Health Service Trust to identify all patients fulfilling *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), criteria for schizophrenia[11] that were taking any of the atypical antipsychotics that were licensed at the time (clozapine, risperidone, olanzapine, sertindole, and quetiapine). The psychiatric service surveyed provides secondary psychiatric care for a population of 67,650, aged between 15 and 64 years.

Initial information about medication and psychiatric diagnosis was obtained from

1. Hospital computer records of medication dispensed from the hospital pharmacy covering a 1-month period prior to the census date. This included all inpatient and some outpatient treatments.
2. Community psychiatric nurses' records.
3. Records from the accounts department of outpatient prescription forms issued by all the psychiatrists in the service, for which local chemists dispensed medication.
4. The medical notes of all patients under the care of the service.

We identified 286 patients with schizophrenia, and, of these, 94 (32.8%) were being treated with atypical antipsychotics. Nineteen patients (6.6%) were taking risperidone, 41 (14.3%) were taking olanzapine, and 34 (11.9%) were taking clozapine. There were no patients on quetiapine or sertindole therapy.

All patients, with the exception of 3, agreed for information to be collected about their service contacts from their records and their nurses, but a significant number declined face-to-face interviews. The percentage of patients from each treatment group agreeing to be interviewed was 42% (8/19) for risperidone, 50% (21/41) for olanzapine, and 71% (22/31) for clozapine. At the second assessment, 3 could not be reached as they were out of contact with the services. Two of these were from the clozapine group and 1 from the olanzapine group.

Psychiatric Assessment

Patients agreeing to be interviewed were seen twice, with a 6-month interval separating the interviews. Psychiatric symptomatology was rated using the Positive and Negative Syndrome Scale (PANSS)[12] and quality of life using the Quality of Life Scale.[13]

Service Use and Cost Measurement

Service use was measured with the Client Service Receipt Inventory,[14] supplemented by hospital records and information by the patient's keyworker. (A keyworker is a member of the psychiatric community team, usually a nurse, that acts as the patient's care coordinator.) The Client Service Receipt Inventory has been used extensively in mental health care research.[15–17] It is based on patient self-report of service use, which had been found to be as good as data obtained from other sources.[18]

An important aspect of the study was to measure services comprehensively.[19] Therefore, in addition to core psychiatric services, we included general health, social, educational, employment, and legal (including criminal justice) services. The level of informal carer support was also measured. Assessments of service utilization were based on the number and the length of contacts during the 4 months prior to the first interview and the 6 months prior to the second. Data were collected primarily by 1 rater (M.L.). Interrater and intrarater reliability were based on a random sample of 10 patients who were interviewed and whose medical notes were examined by a second rater (S.F.).

Unit costs were attached to each service as described by Allen and Beecham.[20] For generic services, national unit costs adjusted for London were used.[21] Unit costs for some other services were based on previous work done at the Institute of Psychiatry.[17] Supported accommodation costs were calculated, but the costs of independent living were not. The cost of medication was based on the British National Formulary[22] estimates converted to U.S. dollars at the exchange rate on December 31, 1998[23]: £1 = US $1.6. The mean monthly acquisition costs for the 3 drugs in this study were US $187 for risperidone, US $270 for olanzapine, and US $368 for clozapine.

Statistical Analyses

The 3 groups were compared on an intention-to-treat basis determined by the medication prescribed on the survey date. The Pearson chi-square test was used to examine the association between medication group and other categorical variables. The Kruskal-Wallis test and 1-way analysis of variance were respectively used for nonnormally and normally distributed interval data. Cost data are generally skewed in their distribution and therefore the Kruskal-Wallis test was used to examine differences between groups for individual cost items. However, this test compares medians rather than means. In order to test for statistically significant differences in the mean total cost between groups, we used the bootstrap method.[24] Bootstrapping involves resampling with replacement from the original data in order to generate estimates that are more likely to be similar to population values. It allows significance tests to be performed in the absence of nonnormal distributions. We generated 1000 new samples from our original data and obtained p values from these.

As this was a naturalistic rather than a randomized design, it was necessary to control for patient characteristics that might have an influence on cost over and above the impact of the medication used. Ordinary least squares multiple regression analysis was used for this purpose. The dependent variable was total formal (i.e., excluding

informal care) service cost for the 6-month period up to the second interview. The independent variables included in the regression analysis were as follows: gender, age, whether the patient had a partner, whether the patient was employed, symptomatology, quality of life, age at first contact with services, number of inpatient days in previous 2 years, number of months on neuroleptic treatment during previous 5 years, highest dose of neuroleptics in previous 5 years, and whether the patient had switched between atypical drugs during the study period.

Although costs were measured for the 4-month period prior to the first interview, we could not use these as a dependent variable because we wished to control for symptomatology and quality of life, neither of which was measured prior to this 4-month period. Therefore, only the 6-month costs prior to the second interview were used in the regression analyses. Symptom and quality of life scores for patients who were not interviewed at the first assessment were predicted using separate regression models with quality of life and symptomatology in turn used as dependent variables, and all other variables listed above were used as independent variables. Two indicator variables were constructed that scored 1 if the quality of life score or symptom score was predicted and 0 if the actual score was used. This allowed us to control for inaccuracy in the prediction process. (A second model was constructed that did not contain the quality of life and symptom variables.)

A further variable was included that scored 1 if the service use data were obtained directly from the patient and 0 if they were obtained from information from medical records or patient's keyworker. This was necessary because it was likely that the latter method would not produce as comprehensive a measure of service use as the former and therefore costs would be underestimated.

All the above variables were entered into the regression model together with 2 indicator variables, which represented the clozapine and olanzapine groups. The risperidone group was used as a reference category. Automatic selection techniques such as stepwise elimination were not used because the variables were specifically chosen as potential cost-affecting factors.

RESULTS

Demographic Information and Psychiatric Histories

General demographic details are summarized in Table 1. There was a statistically significant difference between the groups in sex distribution in that, compared with olanzapine, clozapine and risperidone were used predominantly by male patients. Most patients were single and unemployed.

There were statistically significant differences between the groups in their previous treatment histories. Clozapine patients had an earlier mean age at first contact than patients in the other groups. They also had more than double the number of inpatient days in the previous 2 years than the olanzapine group and more than 4 times that of the risperidone group. The mean highest dose of typical antipsychotics prior to changing to atypical antipsychotics was significantly higher for the clozapine group than for the other groups. Finally, the olanzapine group had a lower mean length of time on treatment with an atypical antipsychotic at the survey date.

Table 1. Demographic Characteristics of 91 Patients With Schizophrenia in a Catchment Area in London

Characteristic	Risperidone (N = 19)	Olanzapine (N = 41)	Clozapine (N = 31)	p Value
Age, mean ± SD, y	38 ± 10	37 ± 9	39 ± 10	NS
Male, N (%)	14 (74)	21 (51)	25 (81)	.02
Single, N (%)	17 (89)	36 (88)	29 (93)	NS
Unemployed, N (%)	17 (89)	36 (88)	30 (97)	NS

Each group had an average of over 10 years of contact with psychiatric services, indicating the long-term nature of the problems for most patients. However, variance within groups was highest for risperidone and least with clozapine, suggesting that patients in the clozapine group had a consistently long contact with services. Higher variance in the risperidone group suggests a more mixed population of patients in terms of their chronicity. This was less so for olanzapine, although it was still markedly different from the clozapine group.

Medication Doses and Drug Changes

At the first assessment, mean ± SD daily medication doses for each group were risperidone, 5.6 ± 1.75 mg; olanzapine, 12.7 ± 5.2 mg; and clozapine, 378 ± 141 mg. There were no statistically significant changes by the second assessment. The clinical characteristics and previous treatment histories are summarized in Tables 2 and 3.

All patients in the risperidone and clozapine groups had been taking typical antipsychotics at some point. However, 5 patients in the olanzapine group had never received a typical antipsychotic. Although the age of these 5 patients ranged from 19 to 44 years, none had been diagnosed as schizophrenic for more than 3 years. Olanzapine therefore was being used as the first-line of treatment in fairly recently diagnosed cases.

The prior use of another atypical antipsychotic showed that, proportionally, around twice as many patients on olanzapine therapy had previously received risperidone than vice versa. The clozapine group showed slightly higher numbers for having been treated with another atypical. In contrast, very few patients previously on clozapine therapy were being treated with another atypical antipsychotic.

A similar pattern was found in the period covered by the study. Changes in medication from the survey date showed 90% (N = 28) of clozapine patients were taking the same medication at the study endpoint, compared with

Table 2. Clinical Characteristics[a]

Characteristic	Risperidone (N = 19)	Olanzapine (N = 41)	Clozapine (N = 31)	p Value
Age at first contact with psychiatric services, y	27 ± 11	26 ± 8	22 ± 5	.02
Psychiatric inpatient days in last 2 years	37 ± 64	83 ± 122	180 ± 199	.002
Highest dose of neuroleptic in last 5 years (1 = 1 g CPZe)[b]	0.6 ± 0.5	0.7 ± 0.7	1.5 ± 1.1	.000
Months on atypical antipsychotic at survey point	15 ± 15	8 ± 6	16 ± 18	.02
PANSS total score	70 ± 17	60 ± 17	69 ± 25	NS
Quality of Life score	42 ± 12	49 ± 26	50 ± 30	NS

[a]All values are mean ± SD. Abbreviation: PANSS = Positive and Negative Syndrome Scale.
[b]CPZe = chlorpromazine equivalent: values for typical antipsychotics converted to daily dose of CPZ according to table from the Bethlem & Maudsley National Health Service Trust Prescribing Guidelines 1999. London, England: Martin Dunitz; 1999.

Table 3. Previous Antipsychotic Treatment (% of cases)

	Risperidone (N = 19)		Olanzapine (N = 41)		Clozapine (N = 31)		
Previous Treatment	N	%	N	%	N	%	p Value
Never received typical antipsychotic	0	0	5	12	0	0	.05
Typical antipsychotics	19	100	36	88	31	100	.04
Risperidone	0	0	16	39	13	43	NS
Olanzapine	3	17	0	0	7	23	NS
Clozapine	1	6	4	10	0	0	NS

63% (N = 12) of risperidone and 62% (N = 25) of olanzapine patients (Pearson $\chi^2 = 6.9$, df = 2, p = .03). All clozapine patients remained on medication to the endpoint, although 2 had reverted to a typical antipsychotic and 1 changed to olanzapine. Seven (17%) of the olanzapine group had changed to clozapine by the end of the study.

Service Utilization

The number of patients in each group who were in contact with specific services is shown in Table 4. The average number of contacts and the range for those actually using these services are given in Table 5. Both tables combine the 4- and 6-month cost periods because there were no substantial differences between the 2.

The vast majority of patients had outpatient contact with a psychiatrist during the 10-month period, and all of those not receiving direct care from a psychiatrist in an outpatient setting had contact with other core services. In all groups, a minority of patients had an inpatient admission over the 10-month period. There was a slight, but not statistically significant, difference between the groups, with around a third of both olanzapine and clozapine patients having at least 1 admission compared with around one quarter of risperidone patients. This difference between the risperidone group and the other 2 was magnified by the number of days spent in hospital.

Table 4. Patients in Contact With Specific Services During the 10-Month Cost Period

	Risperidone (N = 19)		Olanzapine (N = 41)		Clozapine (N = 31)		
Service	N	%	N	%	N	%	p Value
Psychiatric inpatient care	5	26	14	35	9	29	.79
Psychiatrist	19	100	36	88	25	80	.26
Community psychiatric nurse	11	58	29	72	25	80	.09
Psychiatric emergency clinic	1	5	2	5	1	3	.94
Depot clinic	1	5	2	5	1	3	.94
Psychologist	2	10	8	20	2	7	.27
Occupational therapist	4	21	2	5	2	7	.12
Social services	11	58	21	52	18	58	.72
Day care	7	37	17	42	11	35	.89
General health services	8	42	18	45	20	64	.09
General practitioner	8	42	14	35	17	55	.15
Legal	0	0	13	32	3	10	< .01
Others	4	21	11	27	5	17	.59
Informal care	0	0	8	20	5	17	.12
Supported accommodation	3	16	12	30	17	55	.01

Although most patients in each group were in contact with community psychiatric nurses (CPNs), such contact was substantially more likely for those in the clozapine group than those in the risperidone group. The median number of CPN contacts among clozapine patients was twice that of both risperidone and olanzapine patients. The mean number of CPN contacts among the olanzapine patients was particularly affected by an outlier who was voluntarily homeless but in daily contact with a CPN at a drop-in center.

The use of supported accommodation in the clozapine group was around double that of the olanzapine group, and 4 times that of the risperidone group. Clozapine patients also had more contact with general health, primary care, day care, and legal services.

The average level of utilization of social services by patients in the risperidone group was more than double that of the other 2 groups. Similarly, for occupational therapy, the risperidone group had a higher average number of contacts. Numbers here, however, are very low. Occupational therapy services tend to be attached to other facilities such as inpatient and day hospital facilities; to avoid double counting, the category defined here reflects only unique use of this service. Differences largely reflect the use of an occupational therapist as a community keyworker in 1 risperidone case.

Service Costs

The highest service costs for all groups accrued from inpatient admissions, supported accommodation, and medication (Table 6). For each of these, service costs

Table 5. Mean, Median, and Range of Number of Contacts for Those Using Services Over the 10-Month Period

	Risperidone (N = 19)			Olanzapine (N = 41)			Clozapine (N = 31)			
Service	Mean	(Median)	Range	Mean	(Median)	Range	Mean	(Median)	Range	p Value
Psychiatric admission	1.2	(1)	1–2	2.0	(2)	1–3	1.7	(2)	1–3	.55
Psychiatrist	5.0	(5)	1–11	6.8	(6)	1–24	4.6	(4)	1–11	.25
Community psychiatric nurse	14.0	(10)	1–46	22.6	(10)	2–205	26.3	(22)	3–67	.003
Psychiatric emergency clinic	1.0	(1)	0	2.0	(2)	0	1.0	(1)	0	.94
Depot clinic	12.0	(12)	0	8.0	(8)	0	21.0	(1)	0	.95
Psychologist	1.0	(1)	0	7.6	(9)	1–13	2.0	(2)	0	.21
Occupational therapist	9.5	(5.5)	1–26	1.0	(1)	0	1.0	(1)	0	.09
Social services	35.4	(10)	1–242	5.4	(2)	1–58	5.7	(4.5)	1–20	.33
Day care	38.1	(26)	4–84	75.0	(51)	1–247	101.8	(89)	8–314	.8
General health services	5.1	(2)	1–18	5.0	(2.5)	1–21	11.1	(10.5)	1–27	.004
General practitioner	3.4	(2.5)	1–7	3.6	(3)	1–10	3.5	(2)	1–12	.19
Legal	0		0	1.5	(1)	1–5	5.7	(2)	2–13	.008
Others	55.0	(61.5)	5–94	27.0	(14.5)	1–88	53.8	(6)	3–172	.57
Informal care	0		0	55.4	(16)	6–194	29.6	(26)	1–70	.77

Table 6. Mean and Range of Service Costs per Month (US $) (10-month period)

	Risperidone (N = 19)	Olanzapine (N = 41)	Clozapine (N = 31)	
Service	Mean (Range)	Mean (Range)	Mean (Range)	p Value
Psychiatric inpatient care	$451 ($0–$3605)	$1123 ($0–$6576)	$1203 ($0–$6576)	.65
Psychiatrist	18 (3–35)	21 (0–94)	13 (0–35)	.16
Community psychiatric nurse	37 (0–214)	104 (0–1949)	75 (0–200)	.02
Psychiatric emergency clinic	0.2 (0–3)	0.8 (0–16)	0.05 (0–2)	.74
Depot clinic	1 (0–29)	1 (0–19)	2 (0–50)	.95
Medication	162 (8–218)	234 (5–386)	349 (2–386)	< .01
Psychologist	0.5 (0–10)	14 (0–208)	1 (0–19)	.35
Occupational therapist	10 (0–158)	0.2 (0–6)	0.3 (0–6)	.09
Social services	58 (64–321)	13 (0–96)	16 (0–138)	.63
Day care	22 (0–162)	61 (0–947)	64 (0–643)	.87
General health services	8 (0–51)	5 (0–50)	16 (0–78)	.02
General practitioner	11 (0–50)	8 (0–67)	13 (0–46)	.18
Legal	0.3 (0–8)	3 (0–35)	11 (0–317)	.02
Others	11 (0–85)	8 (0–110)	11 (0–200)	.33
Informal carers	0	19 (0–291)	13 (0–210)	.12
24-hour staffed accommodation	259 (0–2368)	397 (0–2368)	850 (0–2368)	.13
Supported hostel	94 (0–1806)	104 (0–1805)	62 (0–1805)	.78
Group home/supported lodgings	0	34 (0–973)	34 (0–973)	.62
Core psychiatric services costs	701 (85–520)	1505 (221–6892)	1685 (408–6961)	< .01
Combined average accommodation costs	354 (0–2368)	534 (0–2368)	946 (0–2368)	.16
Total average costs per month	1144 (85–3725)	2150 (219–7573)	2733 (462–7456)	.01

were highest for the clozapine group and least for the risperidone group. For inpatient admissions, there was little cost difference between the olanzapine and clozapine groups; although both were substantially greater than the costs for the risperidone group, the difference was not statistically significant. Not surprisingly, there was a large difference in medication costs, with those for clozapine being greater than those for the other 2 atypical antipsychotics. Supported accommodation costs varied slightly across the different types of accommodation. Again, the clozapine group incurred the highest monthly cost.

Overall, the total monthly costs between the 3 groups revealed very significant differences: the clozapine group incurred the highest costs and the risperidone group the lowest based on the Kruskal-Wallis test for nonnormally distributed interval data. Bootstrapping showed no statistically significant difference in mean costs between the olanzapine and clozapine groups at the 95% confidence interval (95% CI) (difference in mean costs between the groups = US $583; 95% CI = US –$403 to US $1686). However, there was a significant difference in the comparison between olanzapine and risperidone (difference in mean cost = US $1006; 95% CI = US $221 to US $1850). There was a larger difference between clozapine and risperidone (difference in mean costs = US $1589; 95% CI = US $619 to US $2584).

Regression Analysis

The results of the multiple regression analyses are shown in Table 7. In Model 1, it can be seen that the

Table 7. Regression of Cost on Background Characteristics (N = 82)[a]

	Model 1[b] 4-Month Interview Data Included			Model 2[c] 4-Month Interview Data Excluded		
Variable	B	SE	p Value	B	SE	p Value
Months on atypical[d]	–21	21	.2942	–5	19	.8193
Age, y[d]	27	30	.3608	42	30	.1803
Male[e]	242	456	.5978	74	467	.8749
Age at first contact[d]	–43	29	.1231	–40	30	.1770
Inpatient days (past 2 y)[d]	5	2	.0073	8	2	< .0001
Months on neuroleptics[d]	–14	14	.3098	–5	14	.7269
Maximum neuroleptic dose[d]	53	246	.8289	37	256	.8865
Interviewed at 10 months[e]	1982	1037	.0605	–266	418	.5286
Olanzapine[e]	566	549	.3061	579	518	.2681
Clozapine[e]	246	706	.7277	197	669	.7687
Partner[e]	–1640	709	.0238	–731	686	.2901
Employed[e]	–1966	930	.0383	–1188	597	.0501
Switched antipsychotic[e]	629	480	.1942	509	496	.3081
Quality of life[d]	61	46	.1961	...	...	...
Quality of life predicted[e]	–363	2060	.8606	...	...	...
Symptomatology[d]	61	21	.0036	...	...	...
Symptomatology predicted[e]	2681	1810	.1432	...	...	...
Constant	–5193	2312	.0282	427	813	.6011

[a]Dependent variable = cost at 10-month interview.
[b]Model 1: $R^2 = 0.5758$; adjusted $R^2 = 0.4631$.
[c]Model 2: $R^2 = 0.4869$; adjusted $R^2 = 0.3888$.
[d]Continuous variable.
[e]Dummy variable scoring 1 if condition is met and 0 otherwise.

number of days spent as an inpatient during the previous 2 years was highly predictive of future costs, with every extra day accounting for an extra US $5. Having a partner or being employed each predicted reductions in total costs of over US $1600 compared with living alone and being unemployed. Symptomatology was also very influential: an increase of 1 on the PANSS total score appears to lead to an increase in costs of US $61. Patients in the olanzapine and clozapine groups had costs that were on average US $566 and US $246, respectively, more than those of the risperidone group. At any conventional levels, these differences were not statistically significant. These findings take into account the fact that some symptom and quality of life scores were predicted and some cost information was taken from case notes rather than from interviews. This model could explain 58% of variation in cost.

Model 2 does not contain the quality of life and symptom variables, and as such the amount of variation explained was reduced to 48.7%. However, the other variables had similar impacts as in Model 1, and the cost effects of being in the different medication groups were essentially unchanged. Both models had residuals that followed an approximate normal distribution, and consequently it was not considered necessary to use the bootstrap method.

DISCUSSION

This was not a randomized trial, and it was apparent that there were clear differences between the groups in psychiatric history suggesting more severe and chronic forms of illness for the clozapine group. These patients also had significantly lower age at first contact with services. Substantially higher previous doses of typical antipsychotics and inpatient days over the last 2 years also suggest historically more severe forms of illness for clozapine. This is perhaps to be expected given that clozapine is the prescribed treatment for refractory cases.

There were no statistically significant differences between the groups on either total symptom or quality of life scores. The study also found no significant difference regarding patterns of employment, with most patients being unemployed. The ability to form and maintain relationships did not differ between the 3 groups; in each group, the majority of patients were single. This finding does not lend support to arguments that atypical agents may substantially improve the quality of life of patients by enabling them to return to work or form relationships.

There was a significant difference between numbers of patients remaining on the same drug treatment throughout the study, with the greatest stability being within the clozapine group. There was no difference in the proportion of patients who discontinued risperidone or olanzapine, with nearly half in each group being on different medication at the end of the study period. It is possible that the increased contact with the services dictated by the hematological monitoring requirements of clozapine is conducive to increased long-term compliance. However, it is worth noting that the rates of discontinuation for olanzapine and risperidone seen here are similar to those reported in a 28-week randomized clinical comparison of these 2 drugs (47.5% discontinuation rate) in which patients also had regular and frequent contact with services.[25] The main reasons for discontinuation in that study were unsatisfactory response, patients' decision, and adverse effects. In a study of the use of risperidone in a naturalistic setting, it was found that after an average of 2 years, only 28.9% of patients had remained on this antipsychotic treatment.[26] Again, the 3 main reasons for stopping this medication were lack of satisfactory response, patients' lack of compliance, and side effects. Similarly, in a study that compared the clinical outcome of a nonrandom sample of patents prescribed either olanzapine or risperidone upon hospital admission, only 40% of the risperidone and 13% of the olanzapine treatment group were discharged on the drug originally prescribed.[6] Although we accept that atypical antipsychotics have improved side effect profiles compared with conventional drugs, the rates of discontinuation found in this and other studies suggest that atypical agents are not free of concerns regarding their efficacy and acceptability to patients.

Measures of costs showed a marked difference between the risperidone group and the other 2 groups. Examination of specific services showed that the risperidone group incurred substantially lower costs largely because of less expensive hospitalization, supported accommodation, and medication costs. Lower medication costs were entirely predictable due simply to differences in prices. A comparison of clozapine and the 2 other groups showed that while demographic details were similar, indices of the severity and chronicity of illness were greater in the clozapine group. Higher current admission rates therefore were not unexpected. Reduced rates of admissions for the risperidone compared with the olanzapine group were less predictable. Comparisons of the psychiatric histories of the olanzapine and risperidone groups did not identify any patient characteristics that could account fully for differences in admission rates. The olanzapine group had received slightly higher doses of typical antipsychotics in the past and had been taking olanzapine for a shorter period. These however are tenuous differences if trying to account for admission rates.

The other area of high cost difference was supported accommodation. The higher costs incurred by the clozapine group again fit with its apparent illness pattern. The need for supported accommodation was less for the other 2 groups, but the difference between the olanzapine and risperidone groups again is less easily accounted for.

After controlling for background characteristics, the impact of medication group was different when compared with the uncontrolled results. In the uncontrolled analysis, the mean total costs for the risperidone patients were US $1006 less per month than for the olanzapine patients and US $1589 less per month than for the clozapine patients. In the regression analysis, the costs predicted for the olanzapine group were US $566 per month higher than for the risperidone group, but the clozapine group was on average only US $246 per month more. This implies that the uncontrolled results overestimate the cost differential between risperidone and olanzapine by US $440 and between risperidone and clozapine by US $1343. Of the other factors that had a significant positive effect on cost (symptoms ratings and the number of inpatient days in the last 2 years) and those that had a negative effect (having a partner and being employed), only the number of days spent as an inpatient in the last 2 years differed significantly between the groups. Although the impact of each inpatient day during the last 2 years on costs is small, the differences between the groups are large. Controlling for this variable may therefore help to explain the lower relative cost impact of clozapine in the regression model compared with the initial analysis. The price difference between the clozapine group and risperidone group is very similar to the price difference between the drugs once these other factors are controlled for. However, the price difference between olanzapine and risperidone remains high and unaccounted for in the regression analysis, although this does not reach statistical significance.

In summary, our findings suggest that although clozapine is reserved for patients with a more chronic and severe form of schizophrenia, risperidone and olanzapine are being used in both recently diagnosed and chronic cases. Our study also lends some support to the relative efficacy of clozapine given its relatively low cost impact and the small number of patients changing medication within the study period. The data also suggest that risperidone, as prescribed in ordinary clinical settings, may be a more cost-effective choice than olanzapine. The differences in treatment histories between patients in the risperidone and olanzapine groups were marginal. However, a significant proportion of patients in the olanzapine group (39%) had been previously treated with risperidone and a smaller but considerable number (17%) were switched to clozapine within the study period. This suggests that comparatively more patients in the olanzapine group may have been poor responders than was the case for those taking risperidone. As the cost of the olanzapine group was higher even than that of the clozapine group, one could argue that the use of olanzapine in patients with severe forms of schizophrenia is of questionable value.

This study has a number of limitations. First, the sample size was perhaps not large enough to identify all significant differences between the 3 groups. However, by pooling the patients in the form of the multiple regression model, this limitation is reduced. The sample size did limit the number of explanatory variables that could be included. The highest number of variables included was 17, and this is equal to 5.4 cases per variable, which is the minimum commonly required.[27] Second, the study used a naturalistic rather than a random design, which was appropriate given that we were observing the effects of medication in a routine setting. However, it does mean that underlying differences between the 3 groups were likely. This likelihood has largely been dealt with by using regression analysis, but some biases may remain. Finally, some patients switched or discontinued medication. Again, this is a common occurrence within a routine mental health service, but it does cause difficulties in making definitive links between the medications themselves and the differences observed.

The present study highlights the need for prospective long-term randomized trials comparing the clinical and cost-effectiveness of the atypical antipsychotics to each other in the treatment of schizophrenia. Although atypical antipsychotics have higher acquisition costs than typical neuroleptics, they may result in improved outcomes for schizophrenic patients.[28] With the exception of clozapine, atypical antipsychotics seem to have similar efficacy and tolerability and therefore cost considerations become important in determining optimal use of resources.

Drug names: clozapine (Clozaril and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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