A Comparison of Long-Term Outcome in First-Episode Schizophrenia Following Treatment With Risperidone or a Typical Antipsychotic

Ashok K. Malla, M.B., F.R.C.P.C., D.P.M., M.R.C.Psych.; Ross M. G. Norman, Ph.D., C.Psych.; Derek J. Scholten, B.A. (Hon.); Sandra Zirul, B.A. (Hon.); and Vinod Kotteda, M.B.B.S.

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Background: Most reports assessing the efficacy and tolerability of risperidone have involved patients previously treated with typical antipsychotics. Such patients are more likely to have a greater resistance or intolerance to treatment, thus restricting our interpretation of the impact a new treatment might have on the course of schizophrenia and possibly biasing the results. The present study examines the relative effectiveness of risperidone and typical antipsychotics in patients being treated for their first episode of schizophrenia.

Method: From a cohort of 126 patients, 2 groups of 19 first-episode DSM-III-R/DSM-IV schizophrenia patients matched for age, gender, length of illness, and length of treatment and treated with either a typical antipsychotic or risperidone for a minimum of 1 year were compared on a number of outcome dimensions during their course of treatment and at follow-up. Treatment allocation was not random, and patients were judged to be compliant with medication. Patients treated with typical antipsychotics were followed up for a statistically nonsignificantly longer time (mean = 2.7 vs. 1.9 years).

Results: Six patients (31.6%) from the typical antipsychotic group were admitted to the hospital within the first year following the index admission compared with 1 patient (5.3%) in the risperidone group (admitted at month 14). Patients in the risperidone group showed a statistically significantly lower length of first hospitalization ($p < .01$), utilization of inpatient beds during the course of treatment ($p < .001$), and use of anticholinergic medication ($p < .05$). There were no statistically significant differences in symptom levels, either during the course of treatment or at follow-up; in the use of antidepressant, antianxiety, or mood-stabilizing drugs; or in changes in living circumstances or employment.

Conclusion: These findings confirm at least equal long-term efficacy of typical antipsychotics and risperidone, but a possible advantage for risperidone in decreased service utilization and decreased use of anticholinergic drugs.

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Reprint requests to: Ashok K. Malla, M.B., Department of Psychiatry, University of Western Ontario, LHSC, Victoria Campus, WMCH Bldg., 392 South St., London, Ontario, Canada N6A 4G5 (e-mail: akmalla@uwo.ca).

Although the efficacy of antipsychotic drugs has been well established,[1,2] several limitations restrict their utility in the management of schizophrenia. The newer generation of antipsychotics such as clozapine is reported to have several advantages in efficacy and tolerability compared with typical antipsychotic agents.[3] Risperidone, the first novel antipsychotic drug to be made available since the reintroduction of clozapine, has now been used extensively in the treatment of acute psychotic episodes as well as long-term management of schizophrenia. A number of large multicenter clinical trials conducted since the early 1990s have shown that risperidone is equal or superior to conventional antipsychotics (such as haloperidol) in treating all dimensions of primary psychopathology in schizophrenia.[4–6] The superior tolerability of the novel antipsychotics is also well established.[4,7–9] In addition, some evidence indicates that risperidone, along with other novel antipsychotics, may offer some advantages in reducing inpatient service utilization.[10,11]

The majority of reports on the efficacy and tolerability of risperidone have involved patients who have previously been treated with typical antipsychotics. Using data from patients who have previously been treated with typical antipsychotics restricts our interpretation of the impact a new treatment may have on the course of schizophrenia and may bias the results because of the likelihood of including patients who have either a greater resistance or intolerance to the previous treatments. It is likely that these patients possess characteristics that entail a relatively poor prognosis.

Only a few studies have examined the relative efficacy and tolerability of novel antipsychotics in patients treated

for their first episode of psychosis. Kopala et al.[12] reported a significant reduction in positive and negative symptoms during an open 7-week trial with risperidone in 22 patients with first-episode schizophrenic psychosis. The largest of such recent trials[13] involved 183 patients with a diagnosis predominantly of schizophreniform psychosis. This trial compared treatment with haloperidol and treatment with risperidone, using a randomized, controlled design over a 6-week period. The results showed an almost equal positive and negative symptom response with haloperidol and risperidone, although significant differences were reported in the incidence of extrapyramidal side effects. The doses of haloperidol and, more importantly, of risperidone used in this study would now be considered unnecessarily high for treating first-episode psychosis.

Demonstration of the efficacy and tolerability of a new treatment is only a step toward establishing treatment effectiveness, i.e., the ability of a new treatment to show beneficial effects to an unselected group of patients in any clinical setting. Few studies have examined the effectiveness of novel antipsychotics compared with typical antipsychotics in the long-term management of schizophrenia from the time of the first episode. The relatively long period of time that risperidone has been available (in Canada, since 1993) offers a unique opportunity to examine its comparative effectiveness in the long-term management of schizophrenia from the time of first treatment. Such effectiveness is better examined in relation to multiple dimensions of outcome.

The objective of this retrospective study was to examine the relative effectiveness of risperidone and typical antipsychotics in 2 matched groups of patients with a diagnosis of schizophrenia. Patients were treated with either a typical antipsychotic or risperidone throughout the course of their illness from the time of their first exposure to antipsychotic treatment. The data are derived from a naturalistic clinical sample of patients with a diagnosis of DSM-III-R or DSM-IV schizophrenia who received treatment over a number of years in the same treatment program. The results reported here are part of a larger long-term outcome evaluation of patients enrolled in the program. The effectiveness is assessed on multiple dimensions such as symptoms, side effects, service utilization, and some objective measures related to quality of life.

METHOD

Patients included in this study received comprehensive care in an outpatient, community-oriented treatment program based on the principles derived from a stress-vulnerability model of schizophrenia. Treatment is delivered within a comprehensive model in which medical and psychosocial treatment interventions (family intervention, social skills training, and stress management) are closely integrated and continuity of care is maintained through inpatient and outpatient treatment. Hospitalization is available only as a last resort, and most treatment is provided in the community. A more detailed description of the treatment program is available in an earlier article.[14] There was no reduction in bed availability over the period of 1991 to 1997, when patients included in this study would have had their first hospital admission, and mental health policy in the region had not changed. Physicians working in this program have had ready access to beds, and continuity of care with the same psychiatrist is maintained through both inpatient and outpatient treatment.

The results reported in this article are part of a larger outcome study[14,15] in which 2 cohorts of patients treated initially for their first episode of psychosis with a typical antipsychotic between 1991 and 1997 (N = 96) or with risperidone between 1993 and 1997 (N = 28) were assessed to study the course of their illness. Outcome was assessed on a number of variables including symptoms, extrapyramidal side effects from medication, service utilization, and objective elements of social and living conditions. Patients initially treated with a typical antipsychotic were reassessed after a period ranging from 1 to 8 years. Forty-nine patients (51%) had been switched to a novel antipsychotic owing to lack of response to medication and/or intolerance of typical antipsychotics. Changes observed in these patients after the switch have been reported elsewhere.[15] Of the 28 patients who were initially treated with risperidone between 1993 and 1997 and reassessed over a period ranging from 1 to 4 years, 7 (25%) were eventually switched to clozapine (N = 4) or to a typical antipsychotic (depot injections, N = 3).

A subsample of 19 patients in the program described above who were treated with only risperidone for longer than 1 year were matched with patients in the same program who were treated with only 1 typical antipsychotic throughout the course of their illness. The 2 groups of patients were matched on age, gender, length of illness, and length of treatment. Three sources were used to collect the follow-up data: the Interview for the Retrospective Assessment of the Onset of Schizophrenia (IRAOS),[16] a clinical interview at follow-up, and information extracted from longitudinal clinical data contained in the case records. Data queries arising from a review of case records were clarified through interviews with patients' case managers in the program. The first onset of psychotic symptoms and of any psychiatric symptoms was dated as accurately as possible using the IRAOS. The duration of untreated psychosis was calculated as the time between onset of psychotic symptoms and first antipsychotic drug therapy, and total duration of untreated illness was the time between onset of any psychiatric symptoms and first antipsychotic drug treatment. The IRAOS also provided detailed information regarding periods of relapse, rehospitaliza-

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tion, length and content of outpatient treatments (including pharmacotherapy and psychosocial interventions), employment, and living conditions.

Following the IRAOS, patients were also rated for their level of symptoms at follow-up, extrapyramidal side effects, and quality of life. The Scale for the Assessment of Positive Symptoms (SAPS),[17] the Scale for the Assessment of Negative Symptoms (SANS),[18] and the Brief Psychiatric Rating Scale (BPRS)[19] were used to assess psychotic, negative, and nonpsychotic symptoms. The Extrapyramidal Symptom Rating Scale (ESRS)[20] was used to assess parkinsonism, akathisia, dystonia, and tardive dyskinesia. Patients' current medications, including antipsychotic, anticholinergic, and antidepressant drugs, were also recorded through review of the case records and direct interview with the patients. The time spent in the hospital for each patient was expressed as proportion of total time the patient had been in the program. Data on objective measures of quality of life, such as living circumstances and employment, and utilization of inpatient resources (days in hospital) were also obtained from the above sources and confirmed with patients and their case managers.

Additional longitudinal data on symptom profiles were obtained from case files recorded as part of regular clinical assessments in this program. All clinicians record their findings under the following headings: reality distortion (delusions and hallucinations), disorganization (thought disorder, bizarre behavior, and inappropriate affect), and psychomotor poverty (flat affect, poverty of thought, anhedonia, and avolition). The distinctions among these 3 separate syndromes have been confirmed in a number of studies.[21,22] Based on these recordings, ratings for each of the above 3 syndromes were carried out by an independent assessor (V.K.) to ascertain the proportion of time each syndrome was present during the course of the illness. Interrater reliability of these ratings was established between 2 raters (V.K. and A.K.M.) on 22 case files. Agreement between raters was greatest for reality distortion (interclass correlation coeffecient [ICC] = 0.85) and lowest for disorganization (ICC = 0.65).

The 2 groups were compared on a number of demographic and clinical characteristics at the time of the initiation of treatment, over the treatment period, and at follow-up review. Patients treated with typical antipsychotics (N = 19) received treatment of their first episode of psychosis between 1991 and 1997, and patients in the risperidone group (N = 19) received initial treatment between 1993 and 1997. Patients were followed up for a mean ± SD of 2.7 ± 2.3 years in the typical antipsychotic group and 1.9 ± 1.2 years in the risperidone group. The difference in the length of follow-up was not statistically significant. A majority of patients in both groups received their initial treatment between 1995 and 1997 (60% for typical antipsychotic group and 77% for risperidone group). Outcome over the course of treatment was compared on the following variables: number of days in hospital during index admission; time to first hospitalization following the index admission; number of days spent in hospital as a proportion of total follow-up time; use of anticholinergic, antidepressant, antianxiety, and mood-stabilizing drugs; longitudinal profiles as well as current level of syndromes of reality distortion, disorganization, and psychomotor poverty; and current level of extrapyramidal symptoms. Patients in the 2 groups were also compared on changes achieved in employment and living conditions.

Table 1. Patient Characteristics[a]

Characteristic	Typical Antipsychotic Group (N = 19)	Risperidone Group (N = 19)
Age, y	28.0 (10.3)	28.0 (10.2)
Age at first antipsychotic, y	25.7 (10.5)	26.1 (7.5)
Female, N (%)	5 (26.3)	8 (42.1)
Single, N (%)	16 (85.0)	16 (85.0)
Age at onset of psychosis, y	23.4 (9.5)	23.7 (9.4)
Total duration of untreated psychiatric illness, mo	43.9 (52.0)	52.5 (54.0)
Duration of untreated psychosis, mo	22.5 (47.1)	29.7 (44.5)
Antipsychotic dose, mg[b]	228.7 (161.8)	2.5 (1.5)
Total duration of illness, y	4.6 (4.6)	4.3 (4.0)
Duration of antipsychotic treatment, y	2.7 (2.3)	1.9 (1.2)

[a]Values are expressed as mean (SD) except where noted.
[b]Values for typical antipsychotic group expressed as chlorpromazine equivalents.

RESULTS

A comparison of demographic and clinical characteristics (Table 1) shows that the risperidone patients had a nonsignificantly longer mean duration of untreated psychosis (time between onset of psychotic symptoms and first antipsychotic treatment) and length of total psychiatric symptoms (time between onset of any psychiatric symptoms and first antipsychotic treatment) compared with the typical antipsychotic patients. No between-group differences were found in gender, education, age at onset, length of antipsychotic therapy, and total length of illness. The mean daily antipsychotic dose was relatively low for both groups (typical antipsychotic group mean ± SD chlorpromazine equivalent = 228.7 ± 161.8 mg; risperidone-treated group mean ± SD dose = 2.5 ± 1.5 mg of risperidone). In the typical antipsychotic–treated group, patients received the following medications: haloperidol (N = 12; mean daily dose = 3.1 mg), oral flupenthixol decanoate (N = 2; mean daily dose = 4 mg), zuclopenthixol (N = 2; 150 mg biweekly), trifluoperazine (N = 2; mean daily dose = 12.5 mg), and flupenthixol decanoate (N = 1; 50 mg biweekly). Five (26%) of the 19 patients in the typical antipsychotic group received depot intramuscular medication.

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Clinical Outcomes

Table 2 shows ratings of symptoms at the time of the follow-up assessment. While negative and disorganization symptoms were numerically higher in patients in the typical antipsychotic group, the differences failed to reach statistical significance. Small sample sizes are likely to have restricted the demonstration of significance. Longitudinal profiles of syndromes also showed no significant difference between the 2 groups on the proportion of time each syndrome was present or in the mean rating of the level of each syndrome throughout the follow-up period.

Concomitant medications. The use of anticholinergic drugs was significantly higher in the typical antipsychotic group compared with the risperidone group (Table 2). No such differences were seen in the use of antidepressant, mood-stabilizing, or anxiolytic drugs.

Extrapyramidal side effects. A higher proportion of patients in the typical antipsychotic group compared with the risperidone group (N = 4 [21%] vs. N = 1 [5.3%]) showed at least mild evidence of parkinsonism (rating of 2 or more on any of the parkinsonism items on the ESRS). The most common symptoms were increased rigidity and tremor. Although the mean ratings of parkinsonism were numerically higher for the typical antipsychotic–treated group (mean ± SD rating = 7.2 ± 9.8) compared with the risperidone-treated group (1.9 ± 2.5), these differences did not reach statistical significance. It is noteworthy that none of the patients treated with either typical antipsychotics or with risperidone showed any evidence of akathisia, dystonia, or dyskinesia at the time of the follow-up assessment.

Table 2. Symptom Ratings, Service Utilization, Concomitant Drug Therapy, Employment, and Living Conditions at Follow-Up[a]

	Typical Antidepressant Group (N = 19)		Risperidone Group (N = 19)		
Variable	Mean	SD	Mean	SD	Statistic
Symptom ratings at follow-up					
Total symptoms	23.5	18.9	17.6	18.1	NS
Total SANS score	18.1	13.7	12.2	15.0	NS
Total SAPS score	5.5	9.2	5.5	8.9	NS
Disorganization	4.2	5.9	3.1	4.2	NS
Reality distortion	3.1	6.1	3.8	7.8	NS
Psychomotor poverty	12.4	9.3	9.3	12.1	NS
Service utilization					
Length of first hospital admission, d	28.5	25.2	11	10.25	$p < .01$
Total number of hospital admissions per year	0.84	0.77	0.12	0.33	$p < .001$
% Time spent in hospital	6.6	7.8	0.23	0.64	$p < .002$
	N	%	N	%	
Concomitant drug therapy					
Antidepressants or mood stabilizers	5	26.4	5	26.4	NS
Benzodiazepines	15	79.0	11	57.9	NS
Anticholinergic drugs	16	84.2	4	21.1	$\chi^2 = 4.9$, df = 1, $p < .05$
Employment and living conditions					
Employed	9	47.4	6	31.6	$\chi^2 = 5.4$, df = 1, $p < .05$
Source of income:					
Self	3	18.2	2	11.1	
Family	4	22.7	7	36.9	
Social assistance	7	34.1	5	26.3	
Living with family	12	63.2	16	84.2	$\chi^2 = 13.7$, df = 1, $p < .001$
Living alone	6	31.6	2	10.5	

[a]Abbreviations: SANS = Scale for the Assessment of Negative Symptoms in Schizophrenia, SAPS = Scale for the Assessment of Positive Symptoms in Schizophrenia.

Service utilization. Figure 1 shows time to first hospitalization following discharge from index admission for each group. Of the typical antipsychotic group, 6 patients were admitted to the hospital within the first year, while only 1 patient from the risperidone group was admitted at month 14. There were also highly statistically significant differences between the 2 groups in the length of first hospitalization ($p < .01$), total number of days spent in the hospital subsequent to first admission ($p < .002$), number of hospital admissions per year ($p < .001$), and days spent in the hospital as proportion of total time in treatment ($p < .002$). All differences favored the group treated with risperidone.

We also examined data for mean length of stay in hospital for all patients with a diagnosis of schizophrenia over the period of 1991 to 1997 to ascertain if there had been any change in the pattern of length of hospital admissions. From 1991 to 1997, the average length of stay over this period for patients with the DSM-III-R/DSM-IV diagnostic category of schizophrenia (diagnostic code 295) remained relatively unchanged—between 14 and 16 days—except for 1993, when it increased to 23 days. A closer examination of patients treated in 1993 revealed that this deviation in length of stay was most likely related to a substantial number of patients referred and admitted for clozapine therapy during that year. Clozapine had become available under a publicly funded program in 1991. At the time, however, it was a requirement to admit the patients to the hospital for initiation of clozapine therapy, a requirement that changed in subsequent years.

Employment and Living Conditions

A relatively lower proportion of patients in the risperidone group (N = 6, 31.6%) was in full- or part-time employment compared with the typical antipsychotic group (N = 9, 47.4%) at the time of the review. This difference was significant ($c^2 = 5.4$, df = 1, $p < .02$). There was, however, a higher proportion of patients in the typi-

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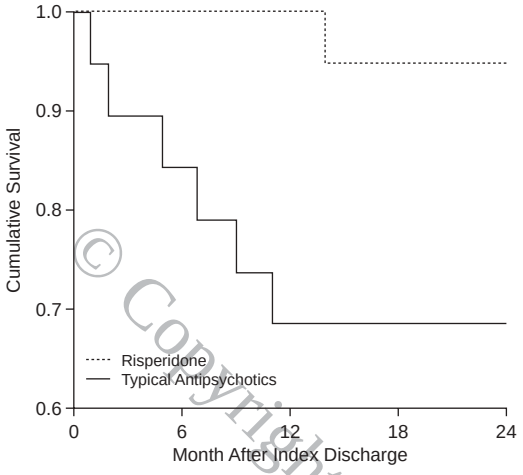
Figure 1. Time to First Hospital Readmission by Treatment Group



cal antipsychotic–treated group (N = 8 [42.9%] vs. N = 5 [26.3%] in the risperidone-treated group) who had been employed prior to treatment ($c^2 = 5.6$, $p < .02$). No significant changes were found in either group posttreatment. The higher proportion of unemployed patients in the risperidone group also included patients who were part- or full-time students. There were no statistically significant differences in living conditions between the groups, with most people living in individual apartments or houses (36/38, 94.7%). A higher proportion of patients in the risperidone group were living with families, and a lower proportion were living alone (N = 16 [84.2%] and N = 2 [10.5%] for the risperidone-treated group vs. N = 12 [63.2%] and N = 6 [31.6%] for the typical antipsychotic–treated group). This difference was significant ($c^2 = 13.7$, $df = 1$, $p < .001$). No statistically significant difference was found between the 2 groups on change over the follow-up period in any of these indices.

DISCUSSION

Two matched samples of patients with first-episode schizophrenia who had been treated with either a typical antipsychotic or risperidone for a period of approximately 2 years showed statistically significant differences in their subsequent utilization of inpatient beds and use of anticholinergic drugs, and statistically nonsignificant differences in the level of disorganization and negative symptoms and parkinsonism. Treatment group assignment was not random, but occurred as part of a clinician's practice; it was also based on accessibility and availability of specific medications. The 2 groups showed no differences in outcome on longitudinal symptom profiles; use of antidepressant, mood-stabilizing, or antianxiety drugs; or social and living conditions. The lack of statistical significance in differences between groups on current level of symptoms and extrapyramidal side effects may be partly an artifact of small sample sizes. The statistically significant difference in service utilization in the absence of a difference between the groups on the longitudinal course of psychotic, disorganization, or negative symptoms may be related to several factors. These are likely to include (1) a possibly quicker response to risperidone therapy resulting in reduced length of first hospitalization, (2) lower compliance rates with typical antipsychotics despite the fact that clinicians judged patients to be compliant, and (3) differences in individual clinicians' practices regarding hospital admissions for patients experiencing either a relapse or side effects. Previous evidence suggests that most patients treated with risperidone, including those with a previous history of treatment, show a positive response in the first 2 weeks at a rate faster than with haloperidol.[23] Subsequent utilization of inpatient bed days has also been shown to be predicted by previous utilization.[24]

Utilization of inpatient resources may have been biased by a sense of optimism about a new medication for patients treated with risperidone. It is equally likely that having fewer concerns about extrapyramidal symptoms may create greater comfort for clinicians in treating patients in outpatient settings following a relatively short first hospital admission. Any differences in the provision of psychosocial interventions and changes in admission policy on length of stay are unlikely explanations. We found no differences in the nature of psychosocial interventions received by each group or any consistent reduction in average length of stay for patients with a diagnosis of schizophrenia who were admitted to the hospital between 1991 and 1997. Further, patients in each group received treatment over a period that largely overlapped, and none of the patients included in the typical antipsychotic group had received initial hospital treatment in 1993, the year with the longest average length of stay.

Although patients were not randomly assigned to the 2 treatment groups, they were matched on a number of key characteristics likely to influence outcome. While there were no significant differences at baseline between the 2 groups, the risperidone-treated group showed a statistically nonsignificant longer duration of untreated psychosis and total illness, factors that are likely to, if anything, negatively influence outcome.[25–27] On the other hand, the typical antipsychotic–treated patients were more often employed prior to treatment and hence would have had an inherently better chance of being employed posttreatment.

Outcome on employment and living conditions in both groups is more likely to reflect premorbid functioning, as neither group showed any real change in any of the related indices. Further, there were more students in the risperidone group, and students were not included in the employed category. Patients in the typical antipsychotic group had been followed up for somewhat longer periods

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and were predominantly male, thus increasing their likelihood of being employed.

Both groups had apparently been taking their respective medication for a considerable period of time. It cannot be assumed that rates of compliance were the same for both groups even though clinicians' judgment of their patients' compliance did not identify high rates of noncompliance in either group. No independent measure was used to assess medication compliance. Patients in each group had been regarded by the clinicians as not in need of switching to another novel antipsychotic (including clozapine) and were regarded to be doing well. The latter assessment is likely to reflect clinicians' perception of the patients' global functioning.

Our findings need to be seen within the limitations imposed by a lack of a priori randomization of treatment exposure for the 2 groups. While there are some advantages to exploring differences in long-term outcome following treatment with typical and novel antipsychotics in a naturalistic clinical sample of first-episode schizophrenia patients, the lack of randomization may restrict generalization of our findings. No reliable data currently support any prediction of differences in long-term outcome for patients treated with typical or novel antipsychotic agents for first-episode schizophrenia. Such questions need to be answered through studies comparing typical and novel antipsychotics in patients with first-episode schizophrenia within a controlled design extending over a lengthy period of time (greater than 1 year). As the use of novel antipsychotics becomes more acceptable, such studies will be necessary to demonstrate their differentially beneficial long-term effect in first-episode patients and compare it with that of typical antipsychotics on several dimensions including, but not limited to, symptoms.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), risperidone (Risperdal), trifluoperazine (Stelazine and others).

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