Risperidone in the Treatment of First-Episode Psychotic Patients: A Double-Blind Multicenter Study

by R.A. Emsley and the Risperidone Working Group

Abstract

An international, multicenter, double-blind study was conducted in 183 patients with a first psychotic episode (provisional schizophreniform disorder or schizophrenia; *DSM–III–R*) treated with flexible doses of risperidone or haloperidol for 6 weeks. At endpoint, 63 percent of risperidone-treated patients and 56 percent of haloperidol-treated patients were clinically improved (≥ 50% reduction in Positive and Negative Syndrome Scale total scores). Risperidone was better tolerated than haloperidol: the severity of extrapyramidal symptoms was significantly lower in the risperidone-treated patients; significantly fewer risperidone-treated patients required antiparkinsonian medication; and significantly fewer discontinued treatment because of adverse events. A post hoc analysis revealed that low doses of these antipsychotics were efficacious in some patients. Furthermore, the severity of extrapyramidal symptoms and the use of antiparkinsonian medications were significantly lower in patients receiving low doses (maximum, ≤ 6 mg/day) than high doses (maximum, > 6 mg/day) of risperidone or haloperidol. These findings are consistent with the suggestion that patients with a first psychotic episode may require low doses of antipsychotic medications. Studies designed specifically to compare low and high doses of antipsychotics are warranted to help optimize treatment for these patients.

Key words: Risperidone, haloperidol, first-episode psychosis.

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Risperidone is both effective and well tolerated in patients with chronic schizophrenia (Chouinard et al. 1993; Marder and Meibach 1994; Peuskens 1995). In the present randomized, controlled study we assessed the efficacy and safety of risperidone in first-episode psychotic patients.

Few prospective studies have been conducted on the effects of antipsychotic agents in first-episode patients during the initial weeks after hospital admission (Scottish Schizophrenia Research Group 1987; Lieberman et al. 1989; Chakos et al. 1992; Syzmanski et al. 1996). In general, these studies indicate that neuroleptic treatment reduces the severity of positive symptoms of schizophrenia but results in a high incidence of extrapyramidal symptoms (Scottish Schizophrenia Research Group 1987; Lieberman et al. 1989; Chakos et al. 1992). Thus it was postulated that an atypical antipsychotic agent such as risperidone, with its low propensity to induce extrapyramidal symptoms at therapeutically effective doses, would be preferable to conventional neuroleptics in the management of these patients. Clinical experience with risperidone has shown that a regimen consisting of low doses (≤ 6 mg/day) and slow titration is essential to optimize patient outcome. The results of the present study support the use of risperidone in patients with a first psychotic episode and are consistent with the recommendation for low doses to optimize outcome for many patients.

Methods

This double-blind, comparative study of risperidone and haloperidol was conducted at 61 psychiatric centers in 10 countries: Australia, Belgium, Canada, France, Germany, Great Britain, Korea, The Netherlands, South Africa, and Sweden.

Patients. Patients were included in the study if they were ages 15 to 45 years; had a diagnosis of provisional schizophreniform disorder (295.40) or schizophrenia without prior treatment according to *DSM–III–R* (American Psychiatric Association 1987); had psychotic symptoms requiring treatment with an oral antipsychotic

Reprint requests should be sent to Dr. R.A. Emsley, Dept. of Psychiatry, University of Stellenbosch, 7505 Tygerberg, South Africa.

agent; had received a maximum of 3 days of emergency treatment for this disorder; had no clinically relevant neurological, electrocardiographic, or laboratory test abnormalities; and had given their informed consent (or that of relatives or guardians) to participate in the study.

Excluded from the study were pregnant or lactating women; women of reproductive age not using adequate contraception; patients with mental illness other than schizophreniform disorder or schizophrenia (according to Axis I of *DSM–III–R*); patients with psychoactive substance abuse (*DSM–III–R* criteria); patients who had received emergency antipsychotic treatment for more than 3 days before study entry or previous depot antipsychotic treatment; patients with clinically significant organic disease; and patients who had participated in clinical trials of investigational drugs within 4 weeks of entry.

Study Procedure. Patients were randomly assigned to receive risperidone or haloperidol for 6 weeks at a starting dose of 2 mg twice daily. The investigator could increase the dose in increments of 2 mg/day according to patients' needs to a maximum of 8 mg twice daily. Initially, patients could receive up to 10 mg twice daily, but this was later reduced to 8 mg twice daily. The dose could be reduced at any time because of clinical response or adverse events; the minimum dose was 2 mg once daily. Whenever possible, patients were kept in the hospital for the first 2 weeks of the study. All antiparkinsonian drugs and psychotropic agents other than the study drugs were discontinued at selection. Antiparkinsonian drugs or benzodiazepines were administered only if essential.

Treatment Efficacy. Treatment efficacy was assessed at weeks 1, 2, 4, and 6 by the Positive and Negative Syndrome Scale (PANSS; Kay et al. 1987) and the Clinical Global Impression scale (CGI; Guy 1976). The PANSS is a validated 30-item scale consisting of three subscales: the positive and negative symptom subscales of 7 items each and the general psychopathology subscale of 16 items. Each item is scored from 1, absent, to 7, extreme. The 18 items that constitute the Brief Psychiatric Rating Scale (BPRS; Overall and Gorham 1962) are included in the PANSS. Clinical improvement, the primary measure of treatment efficacy, was defined a priori as a 50 percent or more reduction in total PANSS scores at endpoint. The percentage of patients who had a 50 percent reduction in total PANSS-derived BPRS scores is also reported. This stringent criterion for clinical improvement was chosen because of the nature of the patient population. Patients with an acute first psychotic episode are likely to have high baseline PANSS scores and to be drug naïve; both factors could increase the likelihood of observing a clinical effect from antipsychotic drug treatment.

The CGI is a global rating of the severity of illness (rated from 1, not ill, to 7, extremely ill) and of the overall change from baseline to endpoint (rated from 1, very much improved, to 7, very much worse).

Treatment Safety. Extrapyramidal symptoms were rated according to the Extrapyramidal Symptom Rating Scale (ESRS; Chouinard et al. 1980). All adverse events that occurred during the trial (including intercurrent disease) and that were mentioned or reported by the patient either spontaneously or in response to questioning were noted and rated by the investigator. At the first and last visit, an electrocardiogram was obtained from each patient and blood samples were drawn for standard laboratory tests. Vital signs were measured weekly.

Statistical Analyses. All enrolled patients were included in the intent-to-treat (endpoint) analysis. A minimum of 77 patients per treatment group as required to detect a 25 percent difference in the primary efficacy endpoint at the 5 percent significance level (two-tailed) with 90 percent power. Analyses were performed to control for country effects. Between-group differences in PANSS total and subscale scores and PANSS-derived BPRS scores were analyzed by the Mann-Whitney *U* test. A two-way analysis of variance (ANOVA) with factors for treatment and country and their interaction was used. If the treatment by country interaction was nonsignificant, the interaction term was omitted from the ANOVA. Nonparametric tests were applied to data not normally distributed (Mann-Whitney *U* test).

The numbers of patients showing a clinical response at endpoint were analyzed using a Cochran-Mantel-Haenszel test for general association, which controlled for differences between countries. CGI severity scores were analyzed by the Cochran-Mantel-Haenszel mean score test and CGI change scores by the Mann-Whitney *U* test. Between-treatment differences in the changes in ESRS scores from baseline to the highest scores recorded during treatment were compared using the Mann-Whitney *U* test, supplemented by the ANOVA model described above. Numbers of patients using antiparkinsonian medications were analyzed by Fisher's exact test. The frequency of other adverse events in each treatment group was compared using Fisher's exact test. A post hoc analysis was used to determine the effects of risperidone and haloperidol treatment at low (maximum, ≤ 6 mg/day) and high (maximum, > 6 mg/day) doses.

Results

One hundred eighty-three patients were recruited for the study, 1 to 43 per country with an average of 18.3 per

country (table 1). Most were young white men, with a median age of 26 years (risperidone group) and 24 years (haloperidol group). Primary diagnoses at study entry were provisional schizophreniform disorder in 93 percent and schizophrenia in 7 percent. The Global Assessment of Functioning indicated severe mental illness in most patients.

The 6-week study was completed by 137 patients (79 in the risperidone group and 58 in the haloperidol group). Six patients (8%) treated with risperidone withdrew because of adverse events (sometimes in combination with other reasons) compared with 15 patients (26%) treated with haloperidol ($p = 0.02$, Fisher's exact test). More patients withdrew from the study because of adverse events or insufficient efficacy, or both, in the haloperidol group (17 patients) than in the risperidone group (9 patients; $p = 0.03$, Fisher's exact test). Other reasons for noncompletion (e.g., ineligibility, intercurrent event, lost to followup, good response, and treatment deviation) were reported in 11 percent of patients in each treatment group. Fifty-five patients (55%) in the risperidone group and 43 (51%) in the haloperidol group were receiving medication when they entered the study. Benzodiazepines were most common (42 in the risperidone group and 31 in the haloperidol group). Duration of trial treatment was 1 to 42 days in both groups. The mean daily dose at endpoint was 6.1 mg of risperidone (range, 2 to 16 mg) and 5.6 mg of haloperidol (range, 2 to 16 mg).

Table 1. Characteristics of patients treated with risperidone or haloperidol

	Risperidone ($n = 99$)	Haloperidol ($n = 84$)
Men/women	68/31	54/30
Age (yr)		
Median	26	24
Range	15–50	16–45
Age at onset of first symptoms of psychosis (yr)		
Median	24	23
Range	15–44	2–45
Race (%)		
White	62	62
Oriental	16	17
Black	12	18
Other	10	4
Primary diagnosis (%)[1]		
Provisional schizophreniform disorder	93	94
Paranoid schizophrenia	4	5
Undifferentiated schizophrenia	2	1
Disorganized schizophrenia	1	0
Level of functioning (%)[2]		
1–20	11	12
21–50	76	73
51–80	13	15

[1] *DSM–III–R,* Axis I.
[2] Global Assessment of Functioning (*DSM–III–R,* Axis V).

Treatment Outcome in Risperidone- and Haloperidol-Treated Patients. Patients in the risperidone and haloperidol groups had comparable PANSS and ESRS baseline scores (tables 2 and 3). At endpoint, 63 percent of the risperidone patients and 56 percent of the haloperidol patients were clinically improved according to total PANSS scores ($p = 0.19$), and 65 percent and 55 percent were improved according to total BPRS scores ($p = 0.08$) (figure 1). PANSS and BPRS total scores and PANSS subscale scores were significantly improved compared with baseline at all time points in both treatment groups ($p < 0.001$); between-treatment differences were not statistically significant (table 2).

At the start of the study most of the patients (69% of each group) had marked to severe illness. At endpoint, most patients (67% of the risperidone group; 63% of the haloperidol group; $p = 0.59$, Cochran-Mantel-Haenszel mean score test, controlling for country) were not ill or had mild symptoms. According to the CGI change scale, at endpoint 71 percent of the risperidone group and 70 percent of the haloperidol group were much or very much improved; 21 percent and 25 percent, respectively, were minimally improved or unchanged; and 8 percent and 5 percent were worse. The between-group differences were not significant ($p = 0.817$, Cochran-Mantel-Haenszel mean score test, controlling for country).

Extrapyramidal symptoms were more severe in the haloperidol group than in the risperidone group on each of the ESRS items (table 3). Significantly greater shifts from baseline to worst score with haloperidol than risperidone were seen on the hyperkinesia factor ($p < 0.01$) and total ESRS (parkinsonism + dystonia + dyskinesia) ($p < 0.05$), as well as on the parkinsonism symptoms of rigidity ($p < 0.05$), gait and posture ($p < 0.05$), tremor ($p < 0.05$), and akathisia ($p < 0.01$). In addition, antiparkinsonian medications were required by significantly more haloperidol- than risperidone-treated patients (75% vs. 50%; $p < 0.001$, Cochran-Mantel-Haenszel test, controlling for country).

Other adverse events. Total adverse events were reported by significantly more haloperidol patients than risperidone patients (90% vs. 78%; $p < 0.05$, Fisher's exact test). Nonextrapyramidal side effects were reported by 59 percent of the risperidone-treated patients and 62 percent of the haloperidol-treated patients. Adverse events other than extrapyramidal symptoms included insomnia

Table 2. Mean (±SEM) baseline PANSS and BPRS scores and change from baseline to endpoint in patients receiving risperidone (R) or haloperidol (H)

		Baseline		Endpoint		
		n^1	Mean	Change[2]	95% CI	p^3
PANSS						
Total	R	98	89.1 ± 1.9	−30.9 ± 2.5	−35.8 – −26.0	0.412
	H	84	89.6 ± 2.2	−29.3 ± 2.7	−34.7 – −23.9	0.683
Positive	R	98	23.7 ± 0.5	−10.6 ± 0.7	−12.0 – −9.2	
	H	84	23.8 ± 0.6	−10.5 ± 0.8	−12.1 – −8.9	0.553
Negative	R	98	21.2 ± 0.7	−5.8 ± 0.7	−7.3 – −4.3	
	H	84	21.2 ± 0.9	−5.3 ± 0.8	−7.0 – −3.7	0.336
GPS	R	98	44.2 ± 1.1	−14.5 ± 1.3	−17.2 – −11.9	
	H	84	44.7 ± 1.3	−13.4 ± 1.5	−16.4 – −10.5	0.410
BPRS						
Total	R	98	51.1 ± 1.1	−17.9 ± 1.4	−20.7 – −15.0	
	H	84	51.5 ± 1.2	−16.8 ± 1.6	−20.0 – −13.6	

Note.—SEM = standard error of the mean; PANSS = Positive and Negative Syndrome Scale; BPRS = Brief Psychiatric Rating Scale; CI = confidence interval; GPS = General Psychopathology Scale.

[1] Number of patients assessed; excludes patients with missing data.
[2] Within-group changes in each variable were significant in both patient groups at all time points ($p < 0.001$, Wilcoxon signed-rank test).
[3] Analysis of variance, F test for treatment effects.

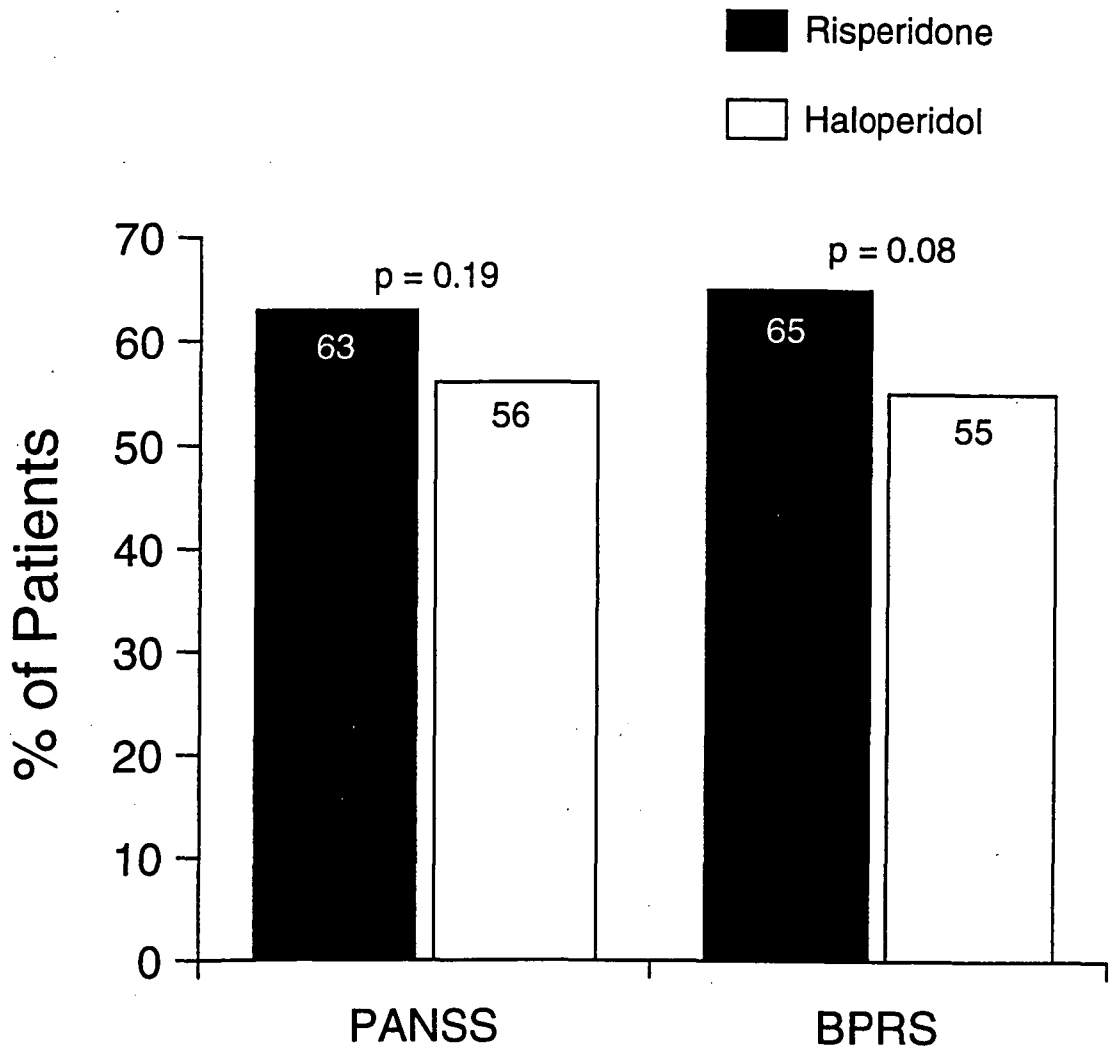
Table 3. Mean baseline ESRS scores and shifts from baseline to worst score in patients receiving risperidone (R) or haloperidol (H)[1]

		Baseline		Shift from Baseline		
		Mean	95% CI	Mean	95% CI	p^2
Questionnaire	R	1.4	0.9–1.9	3.9	3.0–4.9	0.101
	H	1.5	1.0–2.0	5.1	4.0–6.1	
Hypokinesia factor[3]	R	1.4	0.8–2.1	4.5	3.5–5.6	0.273
	H	1.3	0.8–1.8	5.4	4.2–6.5	
Hyperkinesia factor[4]	R	0.3	0.1–0.4	1.4	1.0–1.8	0.007
	H	0.3	0.2–0.5	2.4	1.8–2.9	
Parkinsonism total	R	1.8	1.1–2.5	6.1	4.7–7.5	0.060
	H	1.8	1.1–2.4	8.1	6.4–9.8	
Parkinsonism + dystonia	R	1.8	1.1–2.5	6.3	4.9–7.8	0.060
	H	1.8	1.2–2.5	8.6	6.8–10.4	
Parkinsonism + dystonia + dyskinesia	R	1.9	1.2–2.6	6.5	5.0–7.9	0.046
	H	1.9	1.2–2.5	9.0	7.1–10.9	
CGI Parkinsonism severity	R	0.3	0.1–0.4	1.9	1.5–2.2	0.150
	H	0.4	0.2–0.5	2.2	1.8–2.6	

Note.—ESRS = Extrapyramidal Symptom Rating Scale; CI = confidence interval; CGI = Clinical Global Impression.

[1] ESRS clusters are included if the change from baseline to worst score ≥ 1. Worst scores available for 94 patients in the risperidone group and 80 in the haloperidol group.
[2] Mann-Whitney U test.
[3] *Expressive autonomic movements, bradykinesia, rigidity, gait and posture, and sialorrhea.*
[4] Tremor and akathisia.

Figure 1. Percentages of patients receiving risperidone or haloperidol who were clinically improved at endpoint according to a ≥ 50% reduction in total Positive and Negative Syndrome Scale (PANSS) or PANSS-derived Brief Psychiatric Rating Scale (BPRS) scores



(10% of the risperidone group and 16% of the haloperidol group), headache (10% of each group), agitation (8% and 11%), and anxiety (8% of each group).

Safety measures. No clinically relevant abnormalities were observed in electrocardiograms, heart rate, blood pressure, or laboratory test results.

Post Hoc Analysis—Low- and High-Dose Treatment

Treatment Outcome in Patients Receiving Low and High Doses of Risperidone. Maximum dose data were available for 96 risperidone-treated patients (n = 34, ≤ 6 mg/day; n = 62, > 6 mg/day). A post hoc analysis showed that low-dose risperidone (maximum, ≤ 6 mg/day) was efficacious in many patients and better tolerated than treatment with high-dose risperidone (maximum, > 6 mg/day). Patients receiving low and high doses of risperidone had comparable baseline PANSS and ESRS scores. Patients in both the low- and high-dose groups were clinically improved at endpoint according to total PANSS scores (74% and 59%, respectively). PANSS scores were improved in both groups at most postbaseline time points.

Shifts to worst ESRS scores were significantly greater in the high-dose than the low-dose group on the hypokinesia factor, hyperkinesia factor, total parkinsonism, total ESRS (parkinsonism + dystonia + dyskinesia), and CGI severity of parkinsonism scores ($p < 0.05$, Mann-Whitney U test) (table 4). In addition, antiparkinsonian medications

Table 4. Mean baseline ESRS scores and shifts from baseline to worst score in patients receiving low-dose (≤ 6 mg) or high-dose (> 6 mg) risperidone (R) and haloperidol (H)[1]

	Risperidone						Haloperidol					
		Baseline		Shift from Baseline				Baseline		Shift from Baseline		
	Dose	Mean	95% CI	Mean	95% CI	p^2	Dose	Mean	95% CI	Mean	95% CI	p^2
Questionnaire	≤ 6 mg	1.6	0.5–2.6	2.9	1.4–4.4	0.143	≤ 6 mg	2.1	1.1–3.1	3.0	1.4–4.5	0.0006
	> 6 mg	1.2	0.6–1.8	4.5	3.3–5.6		> 6 mg	1.1	0.6–1.6	6.6	5.2–8.0	
Hypokinesia factor[3]	≤ 6 mg	1.8	0.4–3.2	2.8	1.1–4.5	0.009	≤ 6 mg	1.2	0.4–2.0	3.1	1.4–4.8	0.0002
	> 6 mg	1.2	0.5–1.8	5.4	4.1–6.7		> 6 mg	1.2	0.5–1.9	7.0	5.6–8.5	
Hyperkinesia factor[4]	≤ 6 mg	0.2	−0.1–0.5	0.8	0.4–1.3	0.041	≤ 6 mg	0.3	−0.01–0.7	1.7	0.9–2.5	0.02
	> 6 mg	0.3	0.1–0.4	1.7	1.2–2.2		> 6 mg	0.4	0.1–0.6	2.9	2.1–3.6	
Parkinsonism total	≤ 6 mg	2.1	0.6–3.6	3.8	1.8–5.9	0.004	≤ 6 mg	1.6	0.6–2.6	5.0	2.6–7.4	0.0004
	> 6 mg	1.5	0.8–2.3	7.3	5.6–9.1		> 6 mg	1.8	0.8–2.7	10.4	8.3–12.6	
Parkinsonism + dystonia	≤ 6 mg	2.1	0.6–3.6	3.9	1.9–5.9	0.223	≤ 6 mg	1.6	0.6–2.6	5.4	2.9–7.8	0.0005
	> 6 mg	1.5	0.8–2.3	7.7	5.8–9.5		> 6 mg	1.9	0.9–2.8	11.0	8.6–13.3	
Parkinsonism + dystonia + dyskinesia	≤ 6 mg	2.1	0.6–3.6	3.9	1.9–6.0	0.005	≤ 6 mg	1.7	0.7–2.7	5.5	3.0–8.0	0.0003
	> 6 mg	1.7	0.9–2.4	7.8	5.9–9.8		> 6 mg	1.9	1.0–2.8	11.6	9.0–14.1	
CGI Parkinsonism severity	≤ 6 mg	0.4	0.01–0.8	1.1	0.6–1.7	0.002	≤ 6 mg	0.3	0.1–0.6	1.7	1.1–2.3	0.009
	> 6 mg	0.2	0.03–0.4	2.3	1.8–2.7		> 6 mg	0.4	0.1–0.6	2.7	2.2–3.2	

Note.—ESRS = Extrapyramidal Symptom Rating Scale; CI = confidence interval; CGI = Clinical Global Impression.

[1] ESRS clusters and ESRS parkinsonism items are included if the change from baseline to worst score ≥ 1. Worst scores available for 33 patients in the low-dose risperidone group; 61 in the high-dose risperidone group; 32 in the low-dose haloperidol group; and 47 in the high-dose haloperidol group.
[2] Mann-Whitney *U* test.
[3] Expressive autonomic movements, bradykinesia, rigidity, gait and posture, and sialorrhea.
[4] Tremor and akathisia.

were used by more patients in the high-dose risperidone group than in the low-dose group (40% and 25%, respectively; $p = 0.19$, Cochran-Mantel-Haenszel test, controlling for country). The numbers of patients requiring antiparkinsonian medication increased significantly with the dose ($p = 0.03$; Cochran-Armitage trend test).

Treatment Outcome in Patients Receiving Low and High Doses of Haloperidol. Maximum dose data were available for 81 haloperidol-treated patients ($n = 34$, ≤ 6 mg/day; $n = 47$, > 6 mg/day). Again, patients in both the low- and high-dose groups were clinically improved at endpoint according to total PANSS scores (62% and 55%, respectively). Low doses of haloperidol were better tolerated than higher doses: ESRS shifts to worst scores were greater in the high-dose group on several ESRS clusters (table 4); and antiparkinsonian medications were used by more patients in the high-dose group than in the low-dose group (53% and 46%, respectively; $p = 0.66$, Cochran-Mantel-Haenszel test, controlling for country). The numbers of patients requiring antiparkinsonian medication also increased significantly with the dose of haloperidol ($p = 0.004$; Cochran-Armitage trend test).

Discussion

It is well established that risperidone is a safe and effective antipsychotic agent in patients with chronic schizophrenia. The results of the present study show that it is also efficacious and well tolerated in patients with a first psychotic episode. The severity of psychotic symptoms (PANSS scores) was significantly reduced with risperidone treatment, and the severity of extrapyramidal symptoms (ESRS scores) was significantly lower in patients receiving risperidone than haloperidol. An important issue in the management of these patients was raised in the post hoc analysis. This analysis of patients receiving low and high doses was carried out because the trial was performed before the need for gradual titration and the optimal risperidone dose (≤ 6 mg/day) were well established. Results showed that low-dose risperidone (maximum, ≤ 6 mg/day) was efficacious in some patients and associated with significantly fewer severe extrapyramidal symptoms than high-dose risperidone (maximum, > 6 mg/day). Similar findings were observed in patients receiving haloperidol, a conventional antipsychotic that differs from risperidone in chemical structure, receptor binding profile, and clinical effects. Although illness heterogeneity likely contributed to the breakdown of patients who received low and high doses, the results show that low doses of these agents are efficacious as well as better tolerated in many patients. These data are consistent with the idea that low doses of risperidone, haloperidol, and possibly other antipsychotic agents, may be best for many first-episode patients; these patients appear to be more sensitive to the therapeutic and extrapyramidal effects of antipsychotic medications. A controlled study showed that neuroleptic threshold doses of haloperidol were as efficacious and more tolerable than higher doses in patients with schizophrenia or schizoaffective disorder (McEvoy et al. 1991). A recent open-label study of 22 patients with first-episode schizophrenia showed that low-dose (2–4 mg/day) compared with high-dose (5–8 mg/day) risperidone was associated with a superior outcome (Kopala et al. 1997). Further studies specifically designed to test this hypothesis are clearly warranted.

This dosing issue is particularly important because several studies have shown that patients experiencing a first psychotic episode are at a greater risk of extrapyramidal symptoms than patients with chronic disease. In the 5-week Scottish trial (Scottish Schizophrenia Research Group 1987) of 46 first-episode schizophrenia patients treated with conventional antipsychotic agents (pimozide or flupenthixol), 38 patients (83%) required antiparkinsonian medications; 78 percent and 85 percent of patients received pimozide and flupenthixol, respectively. In the current study, antiparkinsonian medications were used by 75 percent of haloperidol-treated patients and 50 percent of risperidone-treated patients. Lieberman et al. (1989) reported that 79 percent of 53 patients experiencing a first psychotic episode exhibited acute extrapyramidal symptoms during treatment with fluphenazine (20 mg/day). In a further study (Chakos et al. 1992) of first-episode schizophrenia, 41 (62%) of 66 patients treated with fluphenazine experienced acute extrapyramidal symptoms (parkinsonism, akathisia, and dystonia); 85 percent of these patients experienced the extrapyramidal symptoms before the end of the sixth week of treatment. In a study of 29 first-episode schizophrenia patients treated with conventional neuroleptics, Chakos et al. (1994) found that increases in caudate volume were associated with higher doses of neuroleptic and younger age at onset of illness. Keshavan et al. (1994) reported that the caudate nucleus increased in size bilaterally and substantially in treatment-naïve first-episode patients during treatment with conventional neuroleptics. These findings suggest that patients experiencing a first psychotic episode may be at high risk of extrapyramidal symptoms caused by dopamine D_2 antagonism. The results of these trials indicate that first-episode patients may be particularly sensitive to neuroleptic-induced extrapyramidal disorders.

For risperidone, the manufacturer now recommends that treatment should be initiated at 1 mg twice daily for most patients with schizophrenia (Risperdal 1996). An even lower starting dose (≤ 1 mg/day) combined with slow increases (≤ 1 mg/day at intervals of at least 1 week)

may be appropriate in neuroleptic-naïve patients experiencing a first psychotic episode. The current data suggest doses of 3 mg daily or less are appropriate for most of these patients. As always, the target dose should be the lowest efficacious dose.

Nonetheless, even with the dosing regimen used in the present study, the severity of extrapyramidal symptoms was significantly lower with risperidone than with haloperidol. Moreover, significantly fewer risperidone patients required antiparkinsonian medication, and significantly fewer discontinued treatment because of adverse events. These findings in first-episode patients are consistent with results of studies in patients with chronic schizophrenia (Chouinard et al. 1993; Marder and Meibach 1994; Peuskens 1995).

The severity of psychotic symptoms was reduced in both risperidone- and haloperidol-treated patients, and clinical improvement was observed in 63 percent and 56 percent of patients, respectively; between-group differences were not statistically significant. In the Scottish first-episode schizophrenia study (Scottish Schizophrenia Research Group 1987), the patients' mental state improved significantly (reduction in Krawiecka et al. [1977] total scores from baseline) during each week of the 5 weeks of treatment, with no significant between-group differences (23 patients received pimozide and 23 received flupentixol). Positive symptoms also improved significantly, but no change was seen in negative symptoms. In the 53 first-episode patients studied by Lieberman et al. (1989), positive symptom ratings (Endicott and Spitzer 1978) were reduced 50 percent within the first 10 weeks of treatment with fluphenazine, but only a 10 percent reduction was seen in negative symptom scores (Andreasen 1983). In contrast, risperidone and haloperidol effectively reduced both positive and negative symptoms in our patients. The absence of between-group differences in changes in negative symptoms in the present study may have resulted from the low baseline negative symptom scores in both patient groups (table 2). Risperidone was shown to be significantly more effective than haloperidol against negative symptoms in patients with chronic schizophrenia in the North American trial (Marder and Meibach 1994) and in the meta-analysis of these data by Carman et al. (1995) and the path analysis of Möller et al. (1995).

The efficacy of risperidone in ameliorating positive and negative symptoms in patients with a first psychotic episode supports the results of Kopala et al. (1996). This study reported significant positive and negative symptom improvement with risperidone in first-episode psychotic patients: Mean changes in PANSS positive and negative subscale scores and in the positive and negative factors of the five-factor analysis were statistically significant. Prompt and effective amelioration of psychotic symptoms is important because many acutely ill patients are in great distress from frightening and confusing ideas and perceptions. The effective control of symptoms without substantial adverse events, particularly extrapyramidal symptoms, can contribute to long-term compliance and optimal long-term outcome with these patients.

Conclusions

This is the largest study to date of first-episode psychotic patients in whom an atypical antipsychotic was assessed, and it points to some important facts relevant to the treatment of these patients. The study supports the idea that first-episode psychotic patients should receive low doses of risperidone, haloperidol, and possibly other antipsychotic agents. Both risperidone and haloperidol at maximum daily doses of 6 mg or less were efficacious in some patients and better tolerated than maximum daily doses greater than 6 mg. Also, risperidone was at least as effective as haloperidol in ameliorating psychotic symptoms in these acutely ill patients and was better tolerated. Because a patient's first experiences with a drug are crucial in determining compliance, this good tolerance for risperidone may improve the long-term outcome in patients with schizophrenia and other psychoses.

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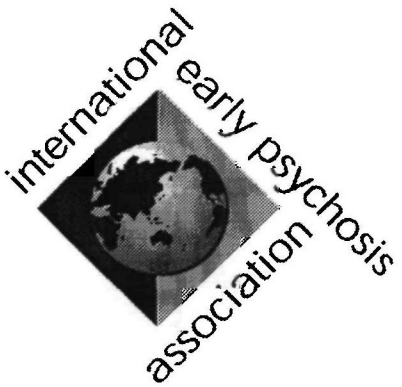
The Authors

R.A. Emsley, M.D., is Professor and Head, Department of Psychiatry, University of Stellenbosch, Tygerberg, South Africa. The psychiatrists who served as investigators in this multicenter trial were as follows: Australia: T. Lambert, Perth; J. McGrath, Brisbane; P. Power and I. Schweitzer, Melbourne. Belgium: G. Bosma and C. Mertens, Sleidinge; A. De Nayer, Montignies-sur-Sambre; J. De Wilde and M. Dierick, St. Denijs-Westrem; J. Peuskens, E. Thys, and S. Wyckaert, Kortenberg. Canada: D. Addington and J. Toews, Calgary, Alberta; L. Beauclair, Montreal, Quebec; A. Labelle, Ottawa, Ontario; G. Remington, Toronto, Ontario. France: O. Blin, Marseilles; C. Gaussares, Bordeaux; B. Lapaquellerie, Cadillac-sur-Garonne. Germany: H. Dilling, S. Drescher, and T. Müller-Thomsen, Lübeck; W. Ettmeier, H. Lauter, P. Martius, D. Messer, S. Modell, F. Müller-Siecheneder, A. Peikert, K. Peschel, and R. Tauscher, Munich; E. Klemm and H.-J. Möller, Bonn; A. Thumulla, Waldbreitbach. Great Britain: K. Brown, Larbert, Scotland; T. Brown, Livingston, Scotland; S. Clark, Perth, Scotland; G. Crocket, A. Hughson, M. Livingston, J. McKane, and L. Watt, Glasgow, Scotland; J. Graham, R. McCreadie, J. Waterhouse, D. Williamson, and E. Wood, Dumfries, Scotland; I. Matson, Paisley, Scotland. Korea: C. Lee and J. Woo, Seoul. The Netherlands: S.P.T. Sinkeler, Meppel. South Africa: G.A.D. Hart and M. Berk, Johannesberg; J.A. Brink, H.G. Russouw, and R.A. Emsley, Tygerberg; C.A. Gagiano and M. Slabber, Bloemfontein; J.L. Roos and H.W. Pretorius, Pretoria. Sweden: M. Mahnfeldt and J.-O. Vahlne, Varberg; P. Osterberg, Hisings-Backa.



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