Treatment of Schizophrenia With Long-Acting Injectable Risperidone: A 12-Month Open-Label Trial of the First Long-Acting Second-Generation Antipsychotic

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Background: The long-term safety and efficacy of long-acting injectable risperidone, the first long-acting second-generation antipsychotic, were evaluated in stable patients with schizophrenia.

Method: After a 2-week run-in period during which patients with DSM-IV schizophrenia received flexible doses of 1 to 6 mg of oral risperidone, patients received injections of 25 mg, 50 mg, or 75 mg of long-acting risperidone every 2 weeks for 12 months. Severity of extrapyramidal symptoms was assessed with the Extrapyramidal Symptom Rating Scale (ESRS), and efficacy was assessed with the Positive and Negative Syndrome Scale (PANSS). This study was conducted from March 29, 1999 to July 19, 2000.

Results: The subjects were 615 patients with schizophrenia who received at least 1 injection of long-acting risperidone. The 12-month trial was completed by 65% of patients. Treatment was discontinued because of adverse events in 5% of patients. Extrapyramidal symptoms as adverse events were reported by 25% of the patients. Severity of extrapyramidal symptoms (according to ESRS scores) was low at baseline and decreased in each of the groups during the 12 months. The other most common adverse events were anxiety in 24%, insomnia in 21%, psychosis in 17%, and depression in 14% of the patients. Little pain was associated with the injections. Severity of symptoms of schizophrenia was improved in each group, with significant reductions in PANSS total scores ($p < .01$) and positive ($p < .01$) and negative ($p < .001$) factor scores.

Conclusion: In terms of both safety and efficacy, symptomatically stable patients with schizophrenia benefit from being switched to long-acting injectable risperidone.

(J Clin Psychiatry 2003;64:1250–1257)

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This study was supported by Johnson & Johnson Pharmaceutical Research and Development, Beerse, Belgium.

Financial disclosure appears at the end of this article.

The authors thank each of the investigators who participated in the trial.

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Many patients with schizophrenia who receive long-term antipsychotic therapy and are judged to be symptomatically stable by their therapists do not achieve optimal recovery.[1,2] Prominent reasons for this partial recovery include poor adherence with oral formulations of antipsychotics and partial responsiveness to the antipsychotic medication. More than 35% of patients begin to show adherence problems during their first 4 to 6 weeks of treatment,[3] and within 2 years, 75% are only partially compliant.[4] The consequences of erratic and often partial adherence with medications can begin with the reappearance of symptoms[5] and reduced functioning and culminate in relapse and rehospitalization.[6] Adherence to medications can be influenced by such factors as the patients' degree of insight into their condition,[7] the convenience of the medication,[7] the side effects of treatment,[8] and the doctor/patient relationship.[9]

Two important advances in the pharmacologic treatment of schizophrenia have attempted to address adherence problems: the introduction of depot antipsychotics in the 1960s and, more recently, the second-generation antipsychotics. Depot antipsychotics have an obvious advantage in reducing daily plasma drug fluctuations and thus have the potential of maximizing efficacy and tolerability while making it easier to monitor medication adherence.[10] Moreover, it has been suggested that they are more efficacious than their oral equivalents.[11] Until now, all depot

antipsychotics have been formulations of conventional agents and share their inadequacies: limited efficacy and poor tolerability, including side effects such as extrapyramidal symptoms (EPS). Depot formulations of conventional agents have also been associated with pain and other adverse effects at the injection site.[12,13] All these factors have limited the use of conventional depot agents.

Second-generation antipsychotics induce significantly less EPS than do conventional agents and also appear to have some efficacy advantages over traditional neuroleptics, for both acute and maintenance treatment. In a recent relapse prevention study,[14] relapse rates during 1 year of treatment were significantly lower in patients receiving risperidone than in patients receiving the most widely used conventional agent, haloperidol.

Long-acting risperidone, the first long-acting injectable formulation of a second-generation antipsychotic, brings together the advantages of a long-acting agent and the advantages of a second-generation antipsychotic. Kane et al.[15] recently demonstrated in a 12-week, double-blind, placebo-controlled study that long-acting risperidone at doses of 25 mg, 50 mg, and 75 mg was significantly more efficacious than was placebo in reducing the severity of schizophrenia symptoms and was well tolerated. In the present study, we evaluated the long-term safety, tolerability, and efficacy of long-acting risperidone.

METHOD

A 12-month, open-label, international (Europe and Canada), multicenter trial was designed to evaluate the long-term safety and tolerability of long-acting risperidone given as an intramuscular injection of 25 mg, 50 mg, or 75 mg every 2 weeks.

During a 2-week run-in period, antipsychotics other than risperidone were discontinued, and patients not currently being treated with risperidone received flexible doses of 1 to 6 mg/day of oral risperidone. At the start of the 12-month study period, patients receiving up to 2 mg of oral risperidone were started on 25 mg of long-acting risperidone, patients receiving more than 2 mg up to 4 mg of the oral drug were started on 50 mg, and patients receiving more than 4 mg up to 6 mg were started on 75 mg. The investigator could adjust the dose of long-acting risperidone whenever deemed necessary. Patients received supplementary oral risperidone (1–6 mg, as determined by the investigator) for the first 2 or 3 weeks of the 12-month study period. Temporary oral supplementation was also permitted during the remainder of the trial when considered by the investigator to be clinically necessary for the treatment of breakthrough psychosis.

The trial was conducted in accordance with current International Conference on Harmonisation-Good Clinical Practice guidelines and the Declaration of Helsinki and its subsequent revisions.

Patients

Subjects were patients aged over 18 years with a diagnosis of schizophrenia according to DSM-IV criteria.[16] Each patient had received a stable dose of an antipsychotic for at least 4 weeks preceding the initial screening and was judged by the investigator to be symptomatically stable. Results of standard clinical laboratory tests were to be within the laboratory's reference range or, if outside this range, judged by the investigator to be not clinically significant.

Patients were excluded from the trial if they were diagnosed as substance-dependent, had tardive dyskinesia or a history of neuroleptic malignant syndrome, had a clinically significant electrocardiogram (ECG) abnormality, or were pregnant (or likely to become pregnant) or lactating. Patients were also excluded if they had a history of severe drug sensitivity or allergy, including sensitivity to risperidone, or had a history of being unresponsive to risperidone. Patients treated with clozapine within 2 months of screening or with a conventional depot antipsychotic within 1 treatment cycle of screening were also ineligible.

Written, informed consent was obtained from each patient or a relative, guardian, or legal representative.

Trial Medication

Long-acting injectable risperidone is an aqueous suspension containing risperidone in a matrix of glycolic acid–lactate copolymer. After intramuscular injection, the copolymer is slowly broken down so that risperidone is gradually released to provide stable blood risperidone levels. The end products of the polymer degradation are carbon dioxide and water. Single-dose studies of long-acting risperidone show that plasma concentrations of the active moiety (risperidone plus 9-hydroxyrisperidone) start to increase 3 weeks after injection, peak levels being reached between weeks 4 and 6.[17] These pharmacokinetics imply that the optimal injection interval to produce the most stable plasma levels over time is 2 weeks and that initial antipsychotic coverage is required during the latency period after the first injection.

Medications other than long-acting risperidone that could be initiated or continued during the trial at the discretion of the investigator were medications prescribed for sleep, antiparkinsonian agents, antidepressants, mood stabilizers, propranolol for akathisia, and benzodiazepines for agitation and insomnia.

Assessments

Spontaneously reported adverse events were recorded by the investigator every 2 weeks. Serious adverse events were defined as those that resulted in death or were life threatening, required hospitalization or prolongation of hospitalization, resulted in persistent or significant disability or incapacity.

Table 1. Background Characteristics by Mode Dose Group in Patients Treated With Long-Acting Risperidone

Variable	25 mg (N = 120)	50 mg (N = 228)	75 mg (N = 267)	Total (N = 615)
Sex, N (%)				
Men	67 (55.8)	164 (71.9)	191 (71.5)	422 (68.6)
Women	53 (44.2)	64 (28.1)	76 (28.5)	193 (31.3)
Race/ethnicity, N (%)				
White	112 (93.3)	210 (92.1)	242 (90.6)	564 (91.7)
Black	1 (0.8)	5 (2.2)	9 (3.4)	15 (2.4)
Asian	1 (0.8)	3 (1.3)	7 (2.6)	11 (1.8)
Hispanic	1 (0.8)	1 (0.4)	3 (1.1)	5 (0.8)
Other	5 (4.2)	9 (3.9)	6 (2.2)	20 (3.3)
Age, y				
Mean ± SE	48.3 ± 1.6	41.6 ± 0.9	39.4 ± 0.7	42.0 ± 0.6
Range	18–74	18–79	18–82	18–84
Schizophrenia type, N (%)				
Paranoid	70 (58.3)	132 (57.9)	180 (67.4)	382 (62.1)
Residual	30 (25.0)	43 (18.9)	26 (9.7)	99 (16.1)
Undifferentiated	17 (14.2)	37 (16.2)	42 (15.7)	96 (15.6)
Disorganized	2 (1.7)	15 (6.6)	16 (6.0)	33 (5.4)
Catatonic	1 (0.8)	1 (0.4)	1 (0.4)	3 (0.5)
Unspecified	0	0	2 (0.7)	2 (0.3)
PANSS total score,[a] mean ± SE	61.9 ± 1.6	67.3 ± 1.2	69.4 ± 1.3	67.1 ± 0.8

[a]Patients with at least 1 post-baseline efficacy assessment: 25-mg group, N = 113; 50-mg group, N = 209; 75-mg group, N = 239; total, N = 561.

Severity of EPS was evaluated by means of the Extrapyramidal Symptom Rating Scale (ESRS),[18] which was completed monthly for the first 3 months and every 3 months thereafter. ESRS total and factor scores[19] are reported. Factor 1 (parkinsonism 1) includes the ESRS items bradykinesia, expressive automatic movements, gait and posture, rigidity, and postural stability. Factor 2 (dyskinesia 1) includes buccolabial movements, jaw movements, lingual movements, and other movements. Factor 3 (dyskinesia 2) includes lower extremity movements, truncal movements, and upper extremity movements. Factor 4 (parkinsonism 2) includes tremor, akathisia, and sialorrhea. Factor 5 (dystonia) includes acute torsion dystonia and nonacute/chronic/tardive dystonia.

Electrocardiograms were performed at screening, baseline, 6 months, and end point. Patients were weighed at screening, 6 months, and end point. Patients rated injection-site pain on a 100-mm visual analogue scale (0 = no pain, 100 = unbearably painful). Investigators evaluated the injection site for redness, pain, swelling, and induration by palpating the injection site. Each item was rated on a scale from 0 (absent) to 3 (severe).

Efficacy was assessed every 3 months by means of the Positive and Negative Syndrome Scale (PANSS)[20,21] and each month by the Clinical Global Impressions-Severity of Illness scale (CGI-S).[22] Clinical improvement was defined a priori as a reduction in total PANSS score of ≥ 20%.

All investigators were trained in the use of the safety and efficacy scales (ESRS and PANSS).

Table 2. Reasons for Early Discontinuation by Mode Dose in Patients Treated With Long-Acting Risperidone

	25 mg (N = 120)		50 mg (N = 228)		75 mg (N = 267)		Total (N = 615)	
Reason	N	%	N	%	N	%	N	%
Total discontinued	28	23.3	70	30.7	117	43.8	215	35.0
Withdrew consent	14	11.7	31	13.6	43	16.1	88	14.3
Insufficient response	2	1.7	7	3.1	39	14.6	48	7.8
Adverse event	5	4.2	13	5.7	12	4.5	30	4.9
Noncompliant	1	0.8	5	2.2	5	1.9	11	1.8
Lost to follow-up	0	0.0	4	1.8	3	1.1	7	1.1
Death	2	1.7	2	0.9	2	0.7	6	1.0
Ineligible	1	0.8	0	0.0	1	0.4	2	0.3
Other	3	2.5	8	3.5	12	4.5	23	3.7

Data Analysis

The primary safety population included all patients who received at least 1 injection of trial medication. The primary efficacy population included all patients who received at least 1 injection of trial medication and had at least 1 post-baseline assessment of efficacy.

Patients were grouped for analysis by mode dose. A last-observation-carried-forward (LOCF) analysis was performed on ESRS and PANSS data. Changes from baseline in PANSS total and factor scores were analyzed by a paired t test. Last-observation-carried-forward and observed-case data are reported.

RESULTS

Of the 663 patients with schizophrenia who were screened for the study, 615 received at least 1 injection of long-acting risperidone (Table 1). Oral antipsychotics had been received previously by 481 of the 615 patients, including risperidone by 369, olanzapine by 36, haloperidol by 35, chlorpromazine by 21, thioridazine by 21, chlorprothixene by 9, zuclopenthixol by 7, perphenazine by 7, promazine by 5, and other antipsychotic agents by 4 or fewer. Depot antipsychotics had been received by 233 of the 615 patients. This study was conducted from March 29, 1999 to July 19, 2000.

The 1-year trial was completed by 65% of the patients. Reasons for discontinuation during treatment with long-acting risperidone were similar in the 3 mode dose groups except for a substantially higher proportion of patients in the 75-mg group who discontinued because of insufficient response (15% versus 2% and 3% in the other 2 groups; Table 2). Fewer than 12 injections of long-acting risperidone were received by 19% of the patients, 12 to 24 injections were received by 23%, and 25 injections were received by 58%.

Adverse Events

Adverse events were reported in 85% of the patients during the trial, the most common being anxiety in 24%, insomnia in 21%, psychosis in 17%, and depression in

Table 3. Treatment-Emergent Adverse Events Reported in 5% or More of Patients Treated With Long-Acting Risperidone in Any One Mode Dose Group

	25 mg (N = 120)		50 mg (N = 228)		75 mg (N = 267)		Total (N = 615)	
Event	N	%	N	%	N	%	N	%
Any adverse event	98	81.7	192	84.2	231	86.5	521	84.7
Anxiety	16	13.3	56	24.6	77	28.8	149	24.2
Insomnia	16	13.3	49	21.5	65	24.3	130	21.1
Psychosis	12	10.0	22	9.6	73	27.3	107	17.4
Depression	16	13.3	28	12.3	45	16.9	89	14.5
Headache	10	8.3	31	13.6	33	12.4	74	12.0
Hyperkinesia	15	12.5	27	11.8	28	10.5	70	11.4
Rhinitis	13	10.8	29	12.7	26	9.7	68	11.1
Fatigue	8	6.7	21	9.2	23	8.6	52	8.5
Dizziness	5	4.2	19	8.3	19	7.1	43	7.0
Extrapyramidal disorder	7	5.8	17	7.5	19	7.1	43	7.0
Injury	5	4.2	14	6.1	19	7.1	38	6.2
Back pain	9	7.5	12	5.3	14	5.2	35	5.7
Hallucination	2	1.7	5	2.2	25	9.4	32	5.2
Somnolence	4	3.3	14	6.1	13	4.9	31	5.0
Agitation	4	3.3	10	4.4	16	6.0	30	4.9
Constipation	5	4.2	8	3.5	17	6.4	30	4.9
Bronchitis	9	7.5	9	3.9	12	4.5	30	4.9
Suicide attempt	4	3.3	7	3.1	18	6.7	29	4.7
Tremor	6	5.0	10	4.4	13	4.9	29	4.7
Influenza-like symptoms	7	5.8	10	4.4	12	4.5	29	4.7
Vomiting	4	3.3	8	3.5	14	5.2	26	4.2
Dyspepsia	2	1.7	9	3.9	14	5.2	25	4.1
Pharyngitis	6	5.0	6	2.6	9	3.4	21	3.4
Arthralgia	6	5.0	5	2.2	5	1.9	16	2.6

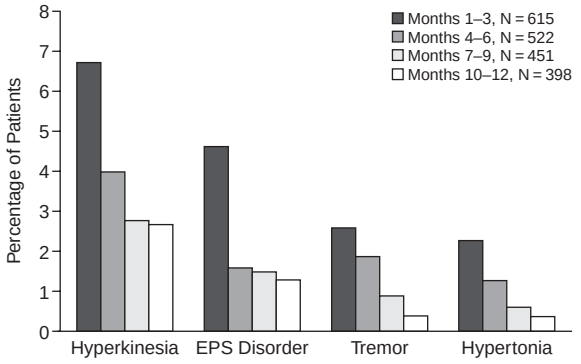
15% (Table 3). The proportions of patients reporting adverse events declined from 68% during months 1–3 of the trial to 43% during months 10–12. The only substantial difference between the mode dose groups in the frequency of adverse events was seen in psychiatric symptoms, reported in 49% of patients in the 25-mg group, 54% of patients in the 50-mg group, and 70% of patients in the 75-mg group. Treatment was discontinued because of adverse events in 5% (30/615) of patients, including 4% (5/120) of the 25-mg group, 6% (13/228) of the 50-mg group, and 4% (12/267) in the 75-mg group.

Extrapyramidal symptoms were reported as adverse events in 25% of all patients, including 21% (25/120) of patients in the 25-mg group, 27% (61/228) of the 50-mg group, and 25% (67/267) of the 75-mg group. Tardive dyskinesia was reported in 4 patients (0.7% of the total). The incidence of EPS was reduced from the first to the fourth quarter of the study (Figure 1).

Severity of EPS (ESRS total and factor scores) was low at baseline and decreased in each of the groups during the 12 months of treatment (Table 4).

No clinically significant changes from baseline to end point in laboratory test results were noted in any of the treatment groups. No significant changes in ECGs were seen over 1 year of treatment. The mean ± SE changes in QTcF (correction factor according to Fridericia[23]) at end point in the 25-mg, 50-mg, and 75-mg mode dose groups

Figure 1. Incidence of Extrapyramidal Symptoms (EPS) by Quarter Spontaneously Reported as Adverse Events in > 2% of Patients During Months 1–3[a]



[a]Symptoms reported during months 1–3 in < 2% of patients were (in decreasing order) dystonia, dyskinesia, tardive dyskinesia, ataxia, muscle contractions, bradykinesia, oculogyric crisis, tetany, tongue paralysis, and hypokinesia.

were 1.9 ± 3.1 milliseconds, –0.4 ± 1.8 milliseconds, and 1.3 ± 2.1 milliseconds, respectively.

The patients experienced small, dose-independent changes in body weight (a mean increase of 1.7 kg [3.7 lb], 2.6 kg [5.7 lb], and 1.9 kg [4.2 lb] in the mode dose groups of 25, 50, and 75 mg, respectively).

Six patients died during the trial: 4 by suicide, 1 of cardiac failure, and 1 of cardiac failure and pulmonary edema. The deaths resulting from cardiac failure were judged to be associated with the patients' underlying cardiac conditions and medical history. Of the 4 patients who committed suicide, all of whom had a diagnosis of paranoid schizophrenia, 1 patient had received 3 injections of long-acting risperidone, 2 had received 16 injections, and 1 had received 22 injections.

Little pain at the injection site was reported by the patients, and the pain ratings decreased during the trial. The median score on the 100-mm visual analogue scale was 10 at the first injection and 5 at the 25th injection. On the investigators' ratings, no injection-site pain was reported in 68% of patients at the first injection and in 80% at the last injection, no redness in 95% and 100% at the first and last injections, respectively, no swelling in 98% and 100%, and no induration in 100% and 93%.

Concomitant Medications

Concomitant medications were received by 88% of the patients during the trial. These included antiparkinsonian agents by 23% of the 25-mg mode dose group, 34% of the 50-mg mode dose group, and 37% of the 75-mg mode dose group and sedatives (e.g., diazepam, lorazepam, oxazepam) by 45%, 54%, and 72% of the mode dose groups, respectively.

Table 4. Mean ± SE Extrapyramidal Symptom Rating Scale (ESRS) Total and Factor Scores at Baseline and Changes at Endpoint (last-observation-carried-forward data) by Mode Dose in Patients Treated With Long-Acting Risperidone[a]

Score	25 mg (N = 120)	50 mg (N = 228)	75 mg (N = 267)	Total (N = 615)
ESRS total				
Baseline	5.1 ± 0.7	8.3 ± 0.6	7.4 ± 0.5	7.3 ± 0.3
Change at endpoint	–1.8 ± 0.4	–3.3 ± 0.4	–2.1 ± 0.4	–2.5 ± 0.2
Parkinsonism 1				
Baseline	2.7 ± 0.3	4.0 ± 0.3	4.0 ± 0.3	3.7 ± 0.2
Change at endpoint	–0.9 ± 0.2	–1.7 ± 0.2	–1.2 ± 0.2	–1.3 ± 0.1
Dyskinesia 1				
Baseline	0.8 ± 0.2	1.4 ± 0.2	1.0 ± 0.1	1.1 ± 0.1
Change at endpoint	–0.2 ± 0.1	–0.5 ± 0.1	–0.2 ± 0.1	–0.3 ± 0.1
Dyskinesia 2				
Baseline	0.3 ± 0.1	0.7 ± 0.1	0.3 ± 0.1	0.5 ± 0.1
Change at endpoint	–0.1 ± 0.1	–0.3 ± 0.1	–0.1 ± 0.1	–0.1 ± 0.0
Parkinsonism 2				
Baseline	1.3 ± 0.2	1.8 ± 0.2	1.8 ± 0.1	1.7 ± 0.1
Change at endpoint	–0.5 ± 0.1	–0.8 ± 0.1	–0.5 ± 0.1	–0.7 ± 0.1
Dystonia				
Baseline	0.2 ± 0.1	0.3 ± 0.1	0.3 ± 0.0	0.3 ± 0.0
Change at endpoint	–0.1 ± 0.0	–0.1 ± 0.1	–0.1 ± 0.1	–0.1 ± 0.0

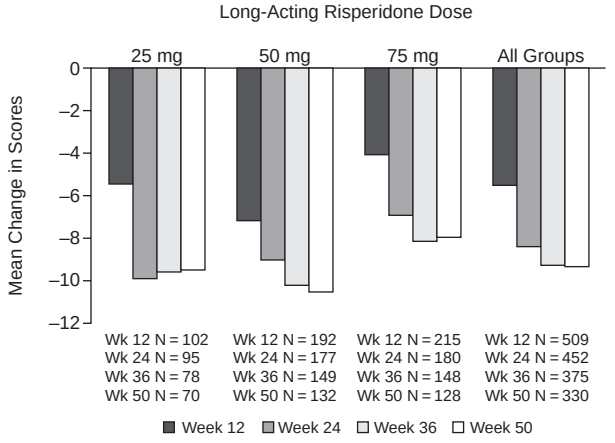
[a]Items included in each factor are listed in the Method section.

Table 5. Mean ± SE Positive and Negative Syndrome Scale (PANSS) Total and Positive and Negative Factor Scores at Baseline and Changes at Endpoint (last-observation-carried-forward data) by Mode Dose in Patients Treated With Long-Acting Risperidone[a]

Score	25 mg (N = 113)	50 mg (N = 209)	75 mg (N = 239)	Total (N = 561)
PANSS total				
Baseline	61.9 ± 1.6	67.3 ± 1.2	69.4 ± 1.3	67.1 ± 0.8
Change at endpoint	–8.0 ± 1.3*	–8.3 ± 1.1*	–3.3 ± 1.1*	–6.1 ± 0.7*
Positive symptoms				
Baseline	16.4 ± 0.6	18.3 ± 0.5	19.9 ± 0.5	18.6 ± 0.3
Change at endpoint	–1.9 ± 0.5*	–2.3 ± 0.4*	–1.1 ± 0.4*	–1.7 ± 0.2*
Negative symptoms				
Baseline	17.7 ± 0.6	19.2 ± 0.5	18.8 ± 0.4	18.8 ± 0.3
Change at endpoint	–2.8 ± 0.4†	–2.9 ± 0.4†	–1.4 ± 0.4†	–2.2 ± 0.2†

[a]Includes patients with at least 1 post-baseline efficacy assessment.
*p < .01 vs. baseline.
†p < .001 vs. baseline.

Figure 2. Mean Improvements From Baseline in PANSS Total Scores at Weeks 12 Through 50[a]



[a]p < .001 vs. baseline at each time point in each group.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

Efficacy

Overall symptom severity (PANSS total scores) and severity of positive and negative symptoms were reduced from baseline to end point in each of the mode dose groups. Last-observation-carried-forward data are shown in Table 5 and observed-case data are shown in Figure 2. The improvements were significant in each mode dose group. At treatment end point (includes scores of early dropouts and trial completers), greater improvements were seen in the 25-mg and 50-mg groups than in the 75-mg group.

Clinical improvement (≥ 20% reduction in PANSS total scores) was seen in 49% of patients: 55% of the 25-mg group, 56% of the 50-mg group, and 40% of the 75-mg group. According to the CGI-S, the proportions of patients who were rated as not ill, very mildly ill, or mildly ill increased from 58% at baseline to 78% at end point in the 25-mg group, from 40% to 65% in the 50-mg group, and from 33% to 44% in the 75-mg group. Only 18% of the patients were rehospitalized during the trial.

DISCUSSION

The results of this long-term study show that symptomatically stable schizophrenia patients can be safely switched from both oral antipsychotic medication and conventional depot antipsychotics to long-acting injectable risperidone. Moreover, the severity of the patients' schizophrenia symptoms was reduced during the 12-month trial.

The discontinuation rate in this trial was low, with 65% of patients completing the trial. This compares favorably with previous trials of similar duration, in which completion rates were 50%[24] or lower.[25] The high completion rate in the present study probably reflects 2 factors: the low incidence of adverse events (only 5% of patients discontinued as a result of an adverse event) and the improvement in symptoms experienced by patients over the course of the 1-year trial. The proportions of patients reporting any adverse event declined over the 12 months.

Extrapyramidal symptoms are among the adverse events of concern among patients receiving antipsychotic

medications. In the present study, severity of EPS (ESRS scores) was low at baseline and was further reduced during treatment with long-acting risperidone (Table 4). Extrapyramidal symptoms reported as an adverse event declined over time (Figure 1). For example, hyperkinesia was reported by 7% of patients during months 1 to 3, by 4% during months 4 to 6, and by fewer than 3% during months 7 to 9 and 10 to 12.

As in other long-term risperidone studies,[15,26] the patients experienced little weight gain. Substantially more weight gain is seen with other second-generation antipsychotics, particularly clozapine (7.5 kg [16.5 lb] over 12 months[27]) and olanzapine (6.26 kg [13.8 lb] after a median treatment of 2.54 years with no significant changes observed after 39 weeks[28]), and many conventional agents[29] than with risperidone.

Little or no injection-site pain or other adverse reaction was reported by the patients and investigators. This is in contrast to conventional depot antipsychotics, which have been associated with pain, bleeding, hematoma, and other injection-site reactions.[12,13] The difference may be related to the oil-based injections that are used for conventional depot antipsychotics. Water-based injections such as long-acting risperidone appear to be less painful than oil-based.[30]

Four patients (all with a diagnosis of paranoid schizophrenia) committed suicide during the trial. The annual suicide rate in this trial was thus 0.55%, which is within the annual rate reported in patients with schizophrenia (between 0.4% and 0.8%).[31] In an analysis of data from 7 clinical trials of psychotic patients treated with second-generation antipsychotics, Khan et al.[32] reported an annual suicide rate of 0.7% in 7630 patients receiving an antipsychotic and 1.8% in 637 patients receiving placebo.

Patients' symptoms were judged by the investigators to be stable while receiving their previous medications at screening. Schizophrenia symptoms were moderate on average, as indicated by mean PANSS total scores below 70[21] and a mean score of 2.7 on the 7-item CGI-S. Nonetheless, patients experienced significant improvement from baseline in PANSS total scores and in positive and negative symptoms. Although mean rating scale score improvements were only moderate, they are probably of clinical relevance because they reflect continuous improvement in a population that was already doing reasonably well at study baseline. It is also interesting to note that the ≥ 20% PANSS score improvement rate found in this study (in 49% of all patients) is comparable to that in the more rigorously controlled short-term double-blind study of long-acting risperidone.[16] According to the CGI-S, a substantially higher proportion of patients was rated as not ill or only mildly ill at end point than at baseline.

The range of doses used in this trial was based on pharmacokinetic data obtained from studies comparing oral risperidone and long-acting injectable risperidone[18] and the central dopamine (D_2) occupancy of long-acting risperidone observed in a study of brain positron emission tomography scans.[33]

The results of the present study suggest that patients in the 75-mg mode dose group were less responsive to treatment than patients in the other 2 groups. For example, 15% of the 75-mg patients discontinued treatment because of an insufficient response, versus 2% and 3% in the 25-mg and 50-mg groups; psychiatric symptoms as adverse events were seen in 70% of the 75-mg patients, versus 49% and 54% of the other 2 groups; concomitant sedatives were received by 72% of the 75-mg patients, versus 45% and 54% of the other 2 groups; and clinical improvement was seen in 40% of the 75-mg patients, versus 55% and 56% of the other 2 groups. This may be explained by the fact that the 75-mg group differed from the other groups at baseline in several ways. A higher proportion of patients in the 75-mg group had a diagnosis of paranoid schizophrenia (67% vs. 58% of the other 2 groups), and fewer had a diagnosis of residual schizophrenia (10% vs. 25% and 19%). Additionally, patients in the 75-mg group were more severely ill: according to the CGI-S, 28% were rated as having marked to severe illness compared with 8% and 18% for the other 2 groups. Patients in the 2 higher dose groups also had higher baseline PANSS scores and higher discontinuation rates.

Investigators adjusted doses of oral risperidone during the 2-week run-in period of this study according to each patient's response. Initial doses of long-acting risperidone were based on the oral doses patients were receiving during the run-in period. The investigators could then adjust the dose of long-acting risperidone during the trial. This procedure can lead to a ceiling effect because of a tendency to increase the dose if no immediate effect is seen and reluctance to reduce the dose if symptoms are controlled and no relevant adverse effects are encountered. It is a methodological artifact of an open-label trial that patients who are more ill get higher doses. Given the dosing flexibility and open nature of this trial, it is therefore not possible to draw conclusions about the dose-response relationships. The present results, however, are consistent with those from a placebo-controlled, randomized, 12-week trial in which the 25-mg and 50-mg doses were efficacious and well tolerated, and increasing the dose beyond 50 mg did not provide additional benefits.[16]

In assessing the long-term efficacy of medication, randomized, placebo-controlled trials are generally considered the most robust method. Such studies, however, are difficult to conduct in schizophrenia patients because of the ethical problems involved in withholding antipsychotic treatment in the long-term. Moreover, selection bias may lead to problems in interpreting and generalizing data from placebo-controlled clinical trials.[31,34] Because the primary goal of the present study was to evaluate the long-term safety of long-acting risperidone, given that the

efficacy of both oral and long-acting risperidone have been established in previous studies,[15,16,22,35] the open-label design without randomization for dose was chosen. This allowed us to recruit a large number of psychopathologically stable schizophrenia outpatients, making this the largest 1-year trial of schizophrenia treatment to date.

The findings that, first, 65% of patients completed the trial (in contrast to the lower completion rates in other oral and depot long-term studies[24,25,36]) and, second, only 18% of patients across all dose groups had to be rehospitalized during the study period are strong indirect evidence of the efficacy and acceptance of the long-acting risperidone formulation. This trial was not designed to study relapse, and no relapse criteria were prospectively defined. When hospitalization is used as a proxy for relapse, the proportion of patients who were rehospitalized during the trial (18%) compares favorably with the 21% to 34% reported with conventional long-acting antipsychotics.[37,38]

CONCLUSIONS

Results of this long-term study indicate that schizophrenia patients with stable symptoms can achieve further improvement in terms of both safety and efficacy by being switched to long-acting risperidone. This new formulation of risperidone represents a significant advance in the long-term treatment of patients with schizophrenia, enabling patients to achieve a better level of symptom control with no compromise to safety or tolerability.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril and others), diazepam (Valium and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), oxazepam (Serax and others), perphenazine (Trilafon and others), propranolol (Inderal and others), risperidone (Risperdal).

Financial disclosure: Dr. Fleischhacker has been a consultant to Johnson & Johnson; received grant/research support from Johnson & Johnson, Sanofi-Synthelabo, and Eli Lilly; received honoraria from Johnson & Johnson, Bristol-Myers Squibb, Eli Lilly, AstraZeneca, Organon, and Pfizer; and served on the speakers or advisory boards for Fujisawa, Otsuka, Bristol-Myers Squibb, AstraZeneca, Johnson & Johnson, and Pfizer. Dr. Eerdekens and Mr. Karcher are employees of Johnson & Johnson Pharmaceutical Research and Development. Dr. Remington has been a consultant to Pfizer and Akzo Nobel; received grant/research support from Pfizer and Janssen; and served on the speakers or advisory boards for Pfizer, AstraZeneca, and Janssen. Dr. Llorca has been a consultant to Janssen-Cilag and Lilly; received grant/research support from Lilly and Novartis; and served on the speakers or advisory boards for Bristol-Myers Squibb and Lundbeck. Dr. Martin has received grant/research support from Janssen-Cilag, Sanofi-Synthelabo, Novartis, and AstraZeneca.

REFERENCES

1. Kane JM. Pharmacologic treatment of schizophrenia. Biol Psychiatry 1999;46:1396–1408
2. Wyatt RJ. Neuroleptics and the natural course of schizophrenia. Schizophr Bull 1991;17:325–351
3. Johnson D. Long-term drug treatment of psychosis: observations on some current issues. Int Rev Psychiatry 1990;2:341–353
4. Weiden J, Zygmunt A. Medication noncompliance in schizophrenia, pt 1: assessment. J Pract Psychiatry Behav Health 1997:106–110
5. Curson DA, Barnes TR, Bamber RW, et al. Long-term depot maintenance of chronic schizophrenic out-patients: the seven year follow-up of the Medical Research Council fluphenazine/placebo trial, II: the incidence of compliance problems, side-effects, neurotic symptoms and depression. Br J Psychiatry 1985;146:469–474
6. Awad AG, Hogan TP. Subjective response to neuroleptics and the quality of life: implications for treatment outcome. Acta Psychiatr Scand Suppl 1994;380:27–32
7. Smith CM, Barzman D, Pristach CA. Effect of patient and family insight on compliance of schizophrenic patients. J Clin Pharmacol 1997;37: 147–154
8. Bond WS, Hussar DA. Detection methods and strategies for improving medication compliance. Am J Hosp Pharm 1991;48:1978–1988
9. Oehl M, Hummer M, Fleischhacker WW. Compliance with antipsychotic drugs. Acta Psychiatr Scand Suppl 2000;407:83–86
10. Kane JM, Aguglia E, Altamura AC, et al. Guidelines for depot antipsychotic treatment in schizophrenia: European Neuropsychopharmacology Consensus Conference in Siena, Italy. Eur Neuropsychopharmacol 1998;8:55–66
11. Davis JM, Matalon L, Watanabe MD, et al. Depot antipsychotic drugs: place in therapy. Drugs 1994;47:741–773
12. Hay J. Complications at site of injection of depot neuroleptics. BMJ 1995;311:421
13. Bloch Y, Mendlovic S, Strupinsky S, et al. Injections of depot antipsychotic medications in patients suffering from schizophrenia: do they hurt? J Clin Psychiatry 2001;62:855–859
14. Csernansky JG, Mahmoud R, Brenner R. A comparison of risperidone and haloperidol for the prevention of relapse in patients with schizophrenia. N Engl J Med 2002;346:16–22
15. Kane JM, Eerdekens M, Lindenmayer JP, et al. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. Am J Psychiatry 2003;160:1125–1132
16. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
17. Eerdekens M, Rasmussen M, Vermeuzen A, et al. Kinetics and safety of a novel risperidone depot. In: New Research Abstracts at the 153rd Annual Meeting of the American Psychiatric Association; May 13–18, 2000; Chicago, Ill. Abstract NR669:238
18. Chouinard G, Ross-Chouinard A, Annable L, et al. The Extrapyramidal Symptom Rating Scale [abstract]. Can J Neurol Sci 1980;7:233
19. Fleischhacker WW, Lemmens P, van Baelen B. A qualitative assessment of the neurological safety of antipsychotic drugs: an analysis of a risperidone database. Pharmacopsychiatry 2001;34:104–110
20. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
21. Marder SR, Davis JM, Chouinard G. The effects of risperidone on the five dimensions of schizophrenia derived by factor analysis: combined results of the North American trials. J Clin Psychiatry 1997;58:538–546
22. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
23. Aytemir K, Maaraouf N, Gallagher MM, et al. Comparison of formulae for heart rate correction of QT interval in exercise electrocardiograms. Pacing Clin Electrophysiol 1999;22:1397–1401
24. Tran PV, Dellva MA, Tollefson GD, et al. Oral olanzapine versus oral haloperidol in the maintenance treatment of schizophrenia and related psychoses. Br J Psychiatry 1998;172:499–505
25. Dellva MA, Tran P, Tollefson GD, et al. Standard olanzapine versus placebo and ineffective-dose olanzapine in the maintenance treatment of schizophrenia. Psychiatr Serv 1997;48:1571–1577
26. Möller HJ, Gagiano CA, Addington DE, et al. Long-term treatment of chronic schizophrenia with risperidone: an open-label, multicenter study of 386 patients. Int Clin Psychopharmacol 1998;13:99–106
27. Briffa D, Meehan T. Weight changes during clozapine treatment. Aust N Z J Psychiatry 1998;32:718–721
28. Kinon B, Basson B, Gilmore A, et al. Long-term olanzapine treatment: weight changes and weight-related health factors in schizophrenia.

J Clin Psychiatry 2001;62:92–100
29. Ganguli R. Weight gain associated with antipsychotic drugs. J Clin Psychiatry 1999;60(suppl 21):20–24
30. Schou Olesen A, Huttel MS. Local reactions to i.v. diazepam in three different formulations. Br J Anaesth 1980;52:609–611
31. Fleischhacker WW. Methodological challenges in the clinical development of antipsychotic drugs. Curr Opin Psychiatry 2000;13:1–2
32. Khan A, Khan SR, Leventhal RM, et al. Symptom reduction and suicide risk among patients treated with placebo in antipsychotic clinical trials: an analysis of the Food and Drug Administration database. Am J Psychiatry 2001;158:1449–1454
33. Gefvert O, Nyberg S, Persson P, et al. Pharmacokinetics, D2 receptor occupancy, and clinical effects of a long-acting injectable formulation of risperidone in patients with schizophrenia [abstract]. Biol Psychiatry 2001;49(8S):117S
34. Hofer A, Hummer M, Huber R, et al. Selection bias in clinical trials with antipsychotics. J Clin Psychopharmacol 2000;20:699–702
35. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825–835
36. Kane JM, Davis JM, Schooler N, et al. A multidose study of haloperidol decanoate in the maintenance treatment of schizophrenia. Am J Psychiatry 2002;159:554–550
37. Love R, Kelly D, Sherr JD, et al. A comparison of rehospitalization rates between patients treated with atypical antipsychotics and those treated with depot antipsychotics [poster]. Presented at the 37th annual meeting of the American College of Neuropsychopharmacology; December 14–18, 1998; San Juan, Puerto Rico
38. Moore DB, Kelly DL, Sherr JD, et al. Rehospitalization rates for depot antipsychotics and pharmacoeconomic implications: comparison with risperidone. Am J Health Syst Pharm 1998;55(suppl 2):137–152