A 1-Year Double-Blind Study of 2 Doses of Long-Acting Risperidone in Stable Patients With Schizophrenia or Schizoaffective Disorder

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Objective: This study examined the effects of 2 doses of long-acting risperidone injection in patients with schizophrenia or schizoaffective disorder.

Method: This 52-week, prospective, randomized, double-blind, multicenter, international study included clinically stable outpatients with schizophrenia or schizoaffective disorder (DSM-IV criteria). Settings included physicians' offices and clinics. Patients received a fixed dose of long-acting risperidone (25 or 50 mg) every 2 weeks. Primary outcome was time to relapse, defined as either rehospitalization or other exacerbation criteria. Other assessments included the Positive and Negative Syndrome Scale, Clinical Global Impressions-Severity of Illness scale, and functional and quality-of-life measures. Safety was assessed via treatment-emergent adverse events, laboratory tests, and movement disorder rating scales. Data were collected from December 2002 to September 2004.

Results: A total of 324 patients were randomized to 25 mg (N = 163) or 50 mg (N = 161) of long-acting risperidone. Time to relapse was comparable (p = .131) for both groups. Projected median time to relapse was 161.8 weeks (95% CI = 103.0 to 254.2) with 25 mg and 259.0 weeks (95% CI = 153.6 to 436.8) with 50 mg. One-year incidences of relapse were 21.6% (N = 35) and 14.9% (N = 24), respectively (p = .059). Psychiatric hospitalization was the reason for relapse for 16 (10%) in the 25-mg group and 10 (6%) in the 50-mg group. Patients experienced statistically significant but modest improvements at endpoint in most measures (i.e., psychotic symptoms, functioning, movement disorder severity) with both doses, with no significant between-group differences.

Conclusion: In this 1-year study, long-acting risperidone was associated with low relapse and rehospitalization rates, indicating that doses of 25 to 50 mg are appropriate for long-term treatment in schizophrenia.

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Schizophrenia is a chronic illness with a variable course. For most patients, it is characterized by frequent relapses with exacerbation of psychosis and the need for psychiatric rehospitalization.[1] Psychiatric hospitalization is a major concern relevant to patients' quality of life and functioning, as well as overall costs of care. The incidence of relapse has been assessed in multiple long-term studies, which have examined a range of doses, routes of administration, and type of antipsychotic (conventional or atypical). Furthermore, these studies have used differing definitions of relapse, with most defining relapse solely on the basis of need for psychiatric rehospitalization. While these differences limit the ability to compare studies, an examination of relapse and completion rates based on route of administration indicates that 1-year relapse rates with long-acting conventional agents range from 20% to 25%[2–4]; 6-month to 1-year relapse rates associated with oral antipsychotics range from 15% to 35%.[1,5,6] While relapse rates were similar regardless of route of administration, cross-study comparisons suggest that completion rates are generally higher with long-acting conventional agents, ranging from 50% to 65% at 1 year vs. 35% to 60% at 6 months to 1 year for oral antipsychotics.[1–6] These results suggest a potential advantage

for long-acting antipsychotics for continuation of long-term treatment, which is an essential factor in ensuring optimal outcomes.

In fact, it has been shown that noncompliance or partial compliance with antipsychotic treatment is a primary factor in relapse.[7] Recent studies have demonstrated that partial compliance—taking some, but not all of medication as prescribed—is also associated with negative outcomes, including exacerbation of symptoms, increased odds of psychiatric hospitalization, poorer functioning, lower quality of life, and higher hospitalization costs.[8–12] Maintenance treatment with long-acting antipsychotics may improve clinical and functional outcomes by minimizing the daily compliance issues faced by patients taking oral antipsychotics. However, the dosing of antipsychotics, particularly conventional long-acting antipsychotics, has long been a treatment challenge for physicians.[13] Studies have focused on the acute response to treatment and long-term safety. Thus, clinical practice has evolved without the benefit of double-blind data to guide decisions on the doses needed to maintain optimal treatment response during long-term therapy.

Csernansky and colleagues[1] recently compared rates of relapse in stable patients with schizophrenia or schizoaffective disorder treated with oral risperidone or oral haloperidol. They found a lower risk of relapse in risperidone- versus haloperidol-treated patients, suggesting the superior clinical profile of risperidone. The clinical profile of an atypical antipsychotic in a long-acting formulation that provides assured medication delivery may further improve outcomes such as relapse.

Recently, the first long-acting atypical antipsychotic, long-acting risperidone injection, has become available.[14–17] Several short- and long-term studies have provided evidence of its safety and efficacy, as well as information on dosing and the transition of patients from oral to long-acting treatment. Both the 25- and 50-mg doses were superior to placebo, with a more pronounced effect size for the 50-mg dose compared with the 25-mg dose. Additionally, a lower discontinuation rate due to lack of response was observed for the 50-mg dose compared with the 25-mg dose.

We assessed this issue in a longer-term study. The objective of this randomized, double-blind trial was to examine 1-year outcomes in stable patients with schizophrenia or schizoaffective disorder transitioned directly from oral antipsychotics to 1 of 2 doses (25 or 50 mg) of long-acting risperidone injection every 2 weeks. The study was designed to test the hypothesis that the higher dose of long-acting risperidone injection would delay the time to relapse compared with the lower dose. Delaying time to relapse has important benefits, not only for individual patients but also for reducing the societal impact of the disease and its associated costs. Secondary endpoints were employed to study possible changes in quality of life and functioning.

METHOD

This was a 52-week, prospective, randomized, double-blind, multicenter, international study of time to relapse following transition from oral antipsychotic medication to 1 of 2 doses of long-acting risperidone injection every 2 weeks. The study was conducted in the United States, Canada, Argentina, and Chile; settings included physicians' offices and clinics.

Subjects

Included subjects were outpatients, 18 to 70 years of age, with a diagnosis of schizophrenia or schizoaffective disorder according to *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (DSM-IV), criteria. Subjects had to have stable symptoms without hospitalization for worsening symptoms or aggressive behavior during the 4 months before baseline, were medically stable, and were taking a stable dose of oral antipsychotic medication for 4 weeks before baseline. Patients were excluded if they were pregnant or breastfeeding; had been a psychiatric inpatient or had required acute crisis intervention for psychiatric symptoms in the 4 weeks before baseline; were at risk of self-injury, injuring others, or causing significant damage to property; had a positive drug screen at screening or a history of drug or alcohol abuse in the past 6 months via clinician report; had a current daily oral antipsychotic dose > 8 mg/day risperidone equivalents or were receiving treatment with carbamazepine or clozapine; had taken depot antipsychotics or had undergone electroconvulsive therapy in the prior 6 months; were deemed treatment-resistant by the investigator; or had a known hypersensitivity to risperidone or a history of neuroleptic malignant syndrome. After provision of a complete description of the study, and an explanation that subjects could withdraw from the trial at any time and for any reason, written informed consent was obtained from each subject or the subject's relative, guardian, or legal representative.

Trial Medications

After a screening phase during which patients continued on stable doses of their oral antipsychotics, patients were randomly assigned to receive long-acting risperidone injection, 25 or 50 mg, every 2 weeks via intramuscular gluteal injection for a total of 27 visits over a 52-week period. For 2 to 3 weeks after the first dose, patients continued to take their prior oral antipsychotic, allowing attainment of therapeutic plasma levels of risperidone prior to discontinuing oral medication. Only 1 patient who entered the study was not receiving any oral antipsychotic for the 4 weeks before baseline. This patient discontinued long-acting risperidone after 1 injection. All patients were encouraged to receive their long-acting risperidone injection within ± 3 days of their regularly

scheduled visit. Partial/noncompliance with injections was defined as receiving more than 25% of injections outside of the 3-day window between weeks 0 and 50. Rescue medications included lorazepam (up to 6 mg/day) for up to 1 week as clinically indicated for the treatment of agitation, severe restlessness, or psychiatric symptomatology. If lorazepam was not fully effective or if an antipsychotic was indicated, oral risperidone (up to 6 mg/day) could be instituted for up to 1 week. Following any 1-week intervention with either supplemental medication, these medications were discontinued (or, if lorazepam had been prescribed as a prior medication, subjects resumed their baseline dose and frequency) and long-acting risperidone injection treatment was continued as monotherapy.

Outcome Measures

The primary endpoint was time to relapse in the intention-to-treat (ITT) population. Relapse was defined as any 1 of the following after the initial 20 days of the study (the timepoint when long-acting risperidone reaches therapeutic blood levels): psychiatric hospitalization due to worsening symptoms; an increase in the level of psychiatric care needed (e.g., significant crisis intervention to avert hospitalization) and an increase of 25% from baseline in Positive and Negative Syndrome Scale (PANSS) score,[18] occurring within 2 weeks of one another; substantial clinical deterioration, as indicated by a score of 6 or 7 on the Clinical Global Impressions-Severity of Illness scale (CGI-S),[19] deliberate self-injury, suicidal or homicidal ideation that is clinically significant as determined by the investigator, or violent behavior leading to clinically significant injury of another person or property damage; or requirement for more than three 1-week periods of oral risperidone therapy within a 3-month period (after day 21).[1]

Secondary efficacy parameters included the PANSS total score; PANSS factor scores for positive symptoms, negative symptoms, anxiety/depression, disorganized thought, and uncontrolled hostility/excitement per Marder et al.[20]; and the CGI-S. These were evaluated at weeks 0, 4, 8, 12, 18, 24, 30, 36, 42, and 52. Functional assessment utilized the Personal and Social Performance scale (PSP)[21] and the Strauss-Carpenter Level of Functioning scale (LOF),[22] performed at weeks 0, 24, and 52. The PSP is a clinician-rated instrument indicating an overall rating of personal and social functioning.[23] It measures 4 domains of functioning in a single-item score: socially useful activities, including work and study; personal and social relationships; self-care; and disturbing and aggressive behaviors. Ratings of 71 to 100 indicate only mild difficulties; ratings of 31 to 70 indicate varying degrees of disability; and ratings of 0 to 30 indicate functioning so poor that the patient requires intensive support or supervision. The Schizophrenia Quality of Life Scale (SQLS) version 3,[24] a patient-administered self-evaluation scale, was used to assess patient-perceived quality of life. This relatively new clinical tool was employed here to collect further data with regard to its utility and validity.

Safety was assessed via regular monitoring of treatment-emergent adverse events; hematology, biochemistry and urinalyses; physical examinations; and movement disorders (via the Extrapyramidal Symptom Rating Scale [ESRS])[25] and the Abnormal Involuntary Movement Scale [AIMS][19]). Treatment-emergent adverse events were monitored at each study visit; laboratory tests were peformed at screening and weeks 0, 12, 24, 36, and 52, and physical examinations, at screening and week 52. The ESRS was performed at weeks 0, 4, 12, 24, 36, and 52; the AIMS was performed at weeks 0, 24, and 52.

Determination of Sample Size, Randomization, Blinding, and Statistical Analysis

The sample size was based on an estimated relapse rate of 25% in the 50-mg group and 40% in the 25-mg group over a 1-year period. The number of observed relapses required to have an 80% chance of detecting a constant hazard ratio of 0.56 is approximately 96 at the 0.05 significance level with a 2-sided test. Therefore, a total of 256 subjects (128/group) were required over the accrual period of 6 months, with a probability of relapse of 0.375 over the duration of the study. This is higher than cited in the literature with conventional depot antipsychotics, because relapse could occur for reasons in addition to the need for psychiatric rehospitalization, which is the only measure of relapse in many studies.[26] Assuming that approximately 20% of randomized subjects would not complete the study due to reasons other than relapse, the total number of subjects needed was estimated to be 320.

Randomization occurred in permuted blocks of 4. Patients were randomized in a 1:1 ratio to treatment and were stratified by prior oral antipsychotic maintenance dose (average [≤ 4 mg/day risperidone equivalents] or above average [> 4 mg/day risperidone equivalents]) and site. Dose equivalency (Table 1) was generated by an expert panel's interpretation of a systematic review of the literature that took into consideration both preclinical and clinical data. This panel included several experts (Janssen and external) in schizophrenia treatment. Panel members first were surveyed to provide dose equivalencies; based on this input, final dose equivalencies were reached via consensus among the entire group. Drs. Simpson, Lasser, and Gharabawi are authors of this article. Drs. Lasser and Gharabawi are employees of Johnson & Johnson Pharmaceutical Services and Janssen Pharmaceutica, Inc., respectively. (See the Acknowledgments for a list of additional external panel members.)

Each treatment group was assigned an equal number (on average) of patients who had received average and higher-than-average prior antipsychotic doses. Random-

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Table 1. Conversion Table From Oral Antipsychotic to Risperidone Equivalents[a]

REQ	0.25	0.5	1	2	3	4	5	6	7	8
CPZ	31	63	125	250	375	500	625	750	875	1000
FLP	1	1	3	5	8	10	13	15	18	20
HAL	1	1	3	5	8	10	13	15	18	20
LEV	8	16	31	63	94	125	156	188	219	250
LOX	4	8	16	33	49	65	81	98	114	130
MES	13	25	50	100	150	200	250	300	350	400
MOL	3	6	13	25	38	50	63	75	88	100
OLZ	1	2	4	8	11	15	19	23	26	30
PCY	1	2	3	6	9	13	16	19	22	25
PCZ	2	3	6	13	19	25	31	38	44	50
PIM	0	1	1	3	4	5	6	8	9	10
PPZ	3	6	13	25	38	50	63	75	88	100
QUE	38	75	150	300	450	600	750	900	1050	1200
TDZ	31	63	125	250	375	500	625	750	875	1000
TTX	1	3	5	10	15	20	25	30	35	40
TFZ	2	4	8	15	23	30	38	45	53	60
ZIP	8	15	30	60	90	120	150	180	210	240
ZUC	1	3	5	10	15	20	25	30	35	40

[a]Used to determine risperidone equivalents by (1) locating patients' pretrial medication on the left side of the chart, (2) moving across the row to the right to find the current total daily (mg) dose, and (3) moving up to locate the rounded risperidone equivalents. For patients receiving multiple oral antipsychotics, individual risperidone equivalents were added to obtain the total daily risperidone equivalents.

Abbreviations: CPZ = chlorpromazine, FLP = fluphenazine, HAL = haloperidol, LEV = levomepromazine, LOX = loxapine, MES = mesoridazine, MOL = molindone, OLZ = olanzapine, PCY = pericyazine; PCZ = prochlorperazine, PIM = pimozide, PPZ = perphenazine, QUE = quetiapine, REQ = risperidone equivalent, TDZ = thioridazine, TFZ = trifluoperazine, TTX = thiothixene, ZIP = ziprasidone, ZUC = zuclopenthixol.

ization was centralized; randomization codes for the treatment phase were generated by a statistician who was not involved in the study conduct. Treatment groups were assigned through an interactive voice response system.

Double-blinded medication consisted of sealed kits containing 1 vial of double-blind risperidone long-acting microspheres (either 25 or 50 mg), a prefilled syringe of reconstitution vehicle (aqueous diluent), and two 20-gauge needles (1 for reconstitution and 1 for injection, to ensure sterility).

Demographic and baseline characteristics were summarized using frequencies, percentages, and descriptive statistics as appropriate. Time to relapse was analyzed using standard survival methods (Kaplan-Meier curves, compared using log-rank test). Median time to relapse could not be calculated since fewer than 50% of subjects relapsed during the 52 weeks of the trial. Thus, a post hoc median time to relapse was estimated using a parametric regression model assuming log-normal distribution. Efficacy was analyzed in the ITT population (all randomized patients who received at least 1 dose of long-acting risperidone and had relapsed or had at least 1 postbaseline efficacy assessment). Safety was analyzed for study patients who received at least 1 dose of long-acting risperidone injection. All statistical tests were 2-sided with 95% coverage. Paired t tests were used to test significance of within-group changes from baseline. Analysis of covariance (ANCOVA) models tested between-group differences at postbaseline visits for continuous measures, with effects for treatment group, pooled site, baseline value, and/or prior antipsychotic therapy. No adjustment was made for multiple comparisons. Categorical variables were evaluated using the Cochran-Mantel-Haenszel test, with stratification by site and/or prior antipsychotic therapy, or rank tests.

RESULTS

Patients were recruited from December 2002 to September 2003; data were collected up to September 2004. Patient disposition information is provided in Figure 1. Most patients were male (62.3%) and had a diagnosis of schizophrenia (79.6%). The mean duration since first hospitalization was 15.2 years, and there was a mean of 4.8 years since last hospitalization (Table 2). Baseline demographics were comparable between doses and across the prior antipsychotic strata. Most patients were taking oral atypical agents prior to the study (Table 2), and 73 (22.6%) were receiving antipsychotic polypharmacy at study entry. Mean (SD) length of treatment with study medication was 237 (128) days for the 25-mg group and 244 (124) days for the 50-mg group; the mean (SD) time between injections was 13.8 (0.4) days for both groups. Mean (SD) treatment compliance (evaluated in the safety population) was comparable between groups: 91.8% (16.7%) for 25-mg and 89.0% (21.3%) for 50-mg long-acting risperidone injection. Of those patients who took oral risperidone after the first 3 weeks of the study, 32% randomly assigned to 25 mg and 26% of patients randomly assigned to 50 mg of long-acting risperidone injection required supplemental oral risperidone (Table 3).

Relapse (ITT population)

The time to relapse was comparable (p = .131) for the 2 treatment groups (Figure 2). Median time to relapse could not be calculated since fewer than 50% of subjects relapsed over the 52 weeks of the trial. A post hoc analysis using a parametric regression model estimated that projected median time to relapse was 161.8 weeks (95% CI = 103.0 to 254.2) for the 25-mg group and 259.0 weeks (95% CI = 153.6 to 436.8) for the 50-mg group. The 1-year crude incidence of relapse was 21.6% (n = 35) and 14.9% (n = 24) for patients randomly assigned to the 25-mg and 50-mg doses, respectively (p = .059 between groups). Patients on average doses of prior antipsychotics (≤ 4 mg/day risperidone equivalents), and maintained on 25- or 50-mg doses of risperidone, had mean 1-year relapse rates of 17.2% and 8.6%, respectively (p = .027 between groups); time to relapse did not differ significantly between groups (p = .102). Patients on higher-than-average doses of prior antipsychotics, and maintained on 25 or

Figure 1. Patient Flow Diagram

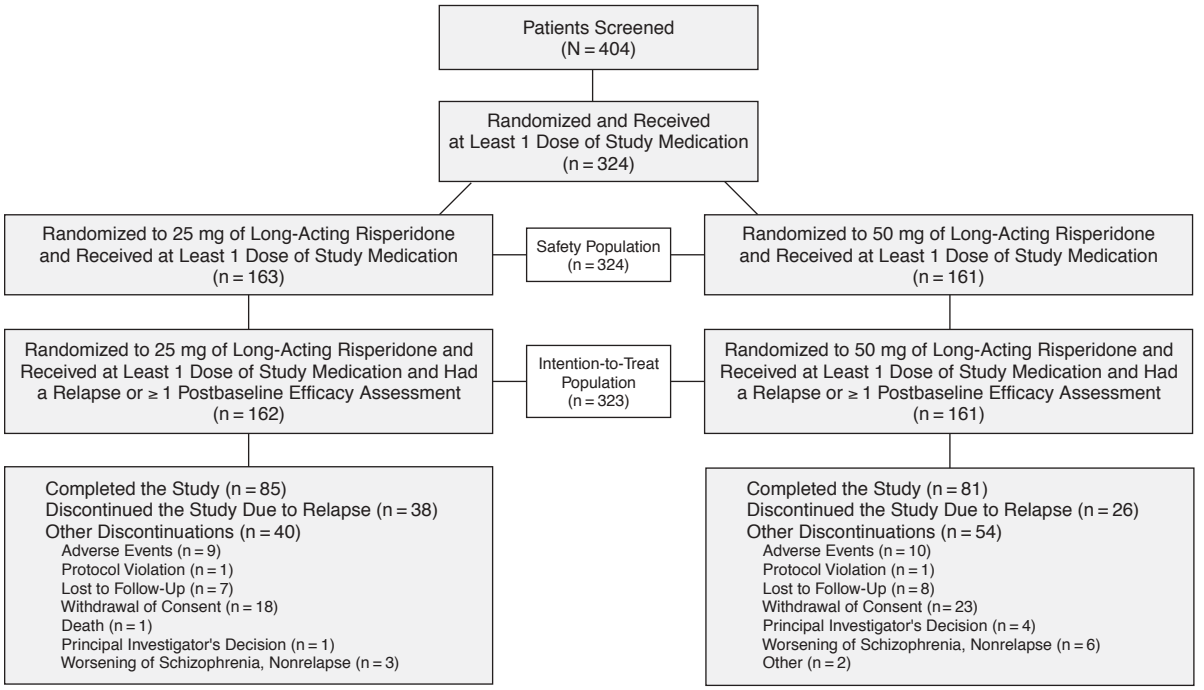

Table 2. Demographic and Baseline Clinical Characteristics of Patients Receiving 25- or 50-mg Doses of Injectable Risperidone (safety population)

	Long-Acting Risperidone Injection		
Parameter	25 mg (n = 163)	50 mg (n = 161)	All Subjects (N = 324)
Age, mean (SD), y	41.7 (12.0)	40.2 (11.9)	40.9 (11.0)
Gender, n (%)			
Female	54 (33.1)	68 (42.2)	122 (37.7)
Male	109 (66.9)	93 (57.8)	202 (62.3)
Race, n (%)			
White	87 (53.4)	73 (45.3)	160 (49.4)
Black	39 (23.9)	45 (28.0)	84 (25.9)
Hispanic	32 (19.6)	30 (18.6)	62 (19.1)
Asian	2 (1.2)	5 (3.1)	7 (2.2)
Other	3 (1.8)	8 (5.0)	11 (3.4)
Diagnosis, n (%)			
Schizophrenia	133 (81.6)	125 (77.6)	258 (79.6)
Schizoaffective disorder	30 (18.4)	36 (22.4)	66 (20.4)
Family history of schizophrenia or schizoaffective disorder, n (%)	32 (19.6)	31 (19.3)	63 (19.4)
Age at onset, mean (SD), y	24.6 (8.8)	26.1 (10.0)	25.4 (9.4)
Duration since initial diagnosis, mean (SD), y	16.9 (11.3)	14.0 (10.7)	15.5 (1.1)
Duration since first psychiatric hospitalization, mean (SD), y	16.9 (12.5)	13.5 (10.1)	15.2 (11.5)
Duration since last psychiatric hospitalization, mean (SD), y	5.2 (7.1)	4.5 (6.1)	4.8 (6.6)
No. of psychiatric hospitalizations, mean (SD)	5.1 (5.7)	4.7 (5.2)	4.9 (5.5)
History of tobacco use, n (%)	104 (63.8)	90 (55.9)	194 (59.9)
History of substance use,[a] n (%)	56 (34.4)	57 (35.4)	113 (34.9)
Prior antipsychotic use,[b] n (%)			
Any	162 (99.4)	161 (100)	323 (99.7)
Aripiprazole	12 (7.4)	6 (3.7)	18 (5.6)
Haloperidol	11 (6.7)	8 (5.0)	19 (5.9)
Olanzapine	44 (27.0)	51 (31.7)	95 (29.3)
Quetiapine	16 (9.8)	22 (13.7)	38 (11.7)
Risperidone	81 (49.7)	64 (39.8)	145 (44.8)
Ziprasidone	8 (4.9)	8 (5.0)	16 (4.9)

[a]Substance use includes alcohol, marijuana, cocaine, heroin, and other.
[b]Prior exposure to oral antipsychotic medication in ≥ 5% of subjects. Percentages add up to > 100% due to polypharmacy in some patients.

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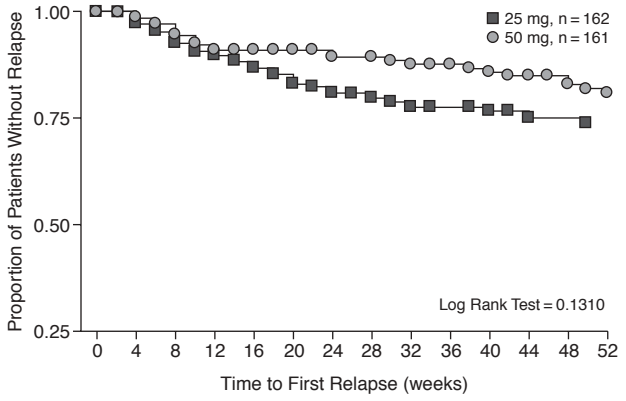
Table 3. Use of Lorazepam or Oral Risperidone as Rescue Medication[a] (ITT population)

Parameter	Long-Acting Risperidone 25 mg (n = 162)	Long-Acting Risperidone 50 mg (n = 161)	All Subjects (N = 323)
Lorazepam			
Change in standing prescription, n (%)	9 (5.6)	3 (1.9)	12 (3.7)
New prescription, n (%)	33 (20.4)	23 (14.3)	56 (17.3)
Duration of new lorazepam, mean (SD) days during 1 year	16.8 (21.5)	20.7 (35.7)	18.5 (28.2)
Dose of new lorazepam in mg, mean (SD)	2.5 (1.4)	2.1 (1.5)	2.3 (1.4)
Risperidone			
Additional oral risperidone, n (%)	52 (32.1)	41 (25.5)	93 (28.8)
Duration of additional oral risperidone, mean (SD) days	12.9 (9.0)	11.8 (5.8)	12.4 (7.6)
Dose of additional oral risperidone in mg, mean (SD)	3.0 (1.5)	2.7 (1.7)	2.9 (1.6)

[a]After first 21 days relative to the first injection for either treatment.
Abbreviation: ITT = intention-to-treat.

Figure 2. Kaplan-Meier Survival Curve Estimates for Relapse (intention-to-treat population)[a]



[a]Patients relapsing during days 1 through 20 were considered censored.

Table 4. Reasons for Relapse (ITT population)[a]

Reason for Relapse, n (%)	Long-Acting Risperidone 25 mg (n = 162)	Long-Acting Risperidone 50 mg (n = 161)	Total (N = 323)
Psychiatric hospitalization	16 (9.9)	10 (6.2)	26 (8.0)
CGI-C score of 6 or 7	9 (5.6)	6 (3.7)	15 (4.6)
Rescue medication	4 (2.5)	5 (3.1)	9 (2.8)
Increase of 25% in PANSS total score and increased level of psychiatric care, occurring within 2 weeks of each other	4 (2.5)	2 (1.2)	6 (1.9)
Violent behavior	2 (1.2)	1 (< 1)	3 (< 1)

[a]Patients relapsing during days 1 through 20 were considered censored.
Abbreviations: CGI-C = Clinical Global Impressions-Change scale, ITT = intention-to-treat, PANSS = Positive and Negative Syndrome Scale.

50 mg of long-acting risperidone injection, had mean relapse rates of 26.7% and 21.3%, respectively (p = .072 between groups); time to relapse did not differ significantly between groups (p = .47). The most common reason that patients relapsed was psychiatric hospitalization, for 9.9% of patients randomly assigned to 25 mg and 6.2% of patients randomly assigned to 50 mg (Table 4). A larger number of patients in the 50-mg group (n = 54) versus the 25-mg group (n = 40) discontinued the study due to reasons other than relapse. Rates of discontinuation for reasons other than relapse were not significantly different between the 2 treatment groups (p = .640).

Symptomatic and Functional Assessments (ITT population)

Patients in both treatment groups experienced statistically significant improvement in symptoms from baseline, as measured by mean PANSS total scores over the course of the study (p < .001; Table 5). Mean (SD) PANSS factor scores improved significantly at endpoint in 4 of 5 factors: positive symptoms, negative symptoms, anxiety/depression, and disorganized thoughts. There was no significant change in hostility/excitement in either group (Table 5). Changes in CGI-S ratings reflected improvements in overall clinical status and were comparable for each of the treatment groups: mean (SD) change at week 52 was –0.6 (0.7) for the 25-mg group (p < .001) and –0.6 (0.8) for the 50-mg group (p < .001). No significant between-group differences were found. Categorical ratings demonstrated baseline-to-endpoint shifts in the proportions of patients rated as mildly ill or better, from 42.6% to 60.7% in the 25-mg group and from 48.4% to 63.2% in the 50-mg group.

Patient functioning, as measured by mean PSP score, was significantly improved for both the 25-mg and 50-mg dose groups at endpoint (p < .05; Table 6). No significant differences were observed between the treatments. At endpoint, 38 (29.2%) of patients in the 25-mg group and 45 (31.7%) of those in the 50-mg group received a rating of good functioning (Table 6). Overall, the proportions of patients who had shifted in category to an improved status were 40.0% in the 25-mg group and 33.8% in the 50-mg group. There were no statistically significant differences between the treatment groups in LOF total scores (4- or 9-item). No significant improvements from baseline to end-

Table 5. PANSS Total and Factor Scores at Baseline and Endpoint (ITT population)

PANSS, mean (SD)	Long-Acting Risperidone Injection 25 mg	50 mg	All Subjects
Total score			
Baseline[a]	66.8 (16.4)	66.1 (16.5)	66.5 (16.4)
Endpoint[b]	62.3 (16.7)	60.6 (17.5)	61.4 (17.1)
Change from baseline	–4.4 (16.2)**	–5.4 (17.5)**	–4.9 (16.8)**
Positive symptoms			
Baseline[a]	18.5 (6.0)	18.4 (6.0)	18.4 (6.0)
Endpoint[b]	17.3 (5.8)	16.8 (6.6)	17.0 (6.2)
Change from baseline	–1.2 (6.1)*	–1.5 (5.6)**	–1.4 (5.9)**
Negative symptoms			
Baseline[a]	17.8 (5.9)	17.5 (5.5)	17.7 (5.7)
Endpoint[b]	15.9 (5.4)	15.6 (5.0)	15.8 (5.2)
Change from baseline	–1.8 (4.7)**	–2.0 (5.5)**	–1.9 (5.1)**
Anxiety/depression			
Baseline[a]	8.8 (3.4)	9.1 (3.2)	9.0 (3.3)
Endpoint[b]	8.1 (3.4)	8.0 (3.3)	8.1 (3.4)
Change from baseline	–0.8 (3.4)*	–1.0 (3.8)**	–0.9 (3.6)**
Disorganized thought			
Baseline[a]	15.7 (4.7)	15.0 (4.6)	15.4 (4.7)
Endpoint[b]	14.9 (4.9)	14.1 (4.4)	14.5 (4.7)
Change from baseline	–0.8 (4.2)*	–0.9 (4.3)*	–0.8 (4.3)**
Uncontrolled hostility/ excitement			
Baseline[a]	6.0 (2.1)	6.1 (2.3)	6.0 (2.2)
Endpoint[b]	6.1 (2.7)	6.0 (2.8)	6.1 (2.8)
Change from baseline	0.2 (2.8)	0.0 (2.7)	0.1 (2.8)

[a]25-mg group, n = 162; 50-mg group, n = 161; all subjects, N = 323.
[b]25-mg group, n = 155; 50-mg group, n = 155; all subjects, N = 310.
*p ≤ .05; **p ≤ .001 vs. baseline; no significant between-group differences.
Abbreviations: ITT = intention-to-treat, PANSS = Positive and Negative Syndrome Scale.

Table 6. Mean PSP Scores and Distributions of Patients Receiving Ratings Reflecting Good, Variable, or Poor Functioning (ITT population)

PSP score	Long-Acting Risperidone Injection 25 mg	50 mg
Baseline		
n	162	161
Mean (SD) score	61.8 (14.8)	62.5 (13.5)
Endpoint		
n	130	142
Mean (SD) score	63.8 (15.0)	64.4 (13.1)
Mean change from baseline at endpoint	2.4 (13.46)*	2.0 (11.2)*
Patients receiving PSP ratings of good, variable, or poor,[a] N (%)		
Baseline	n = 161	n = 161
Good	41 (25.5)	48 (29.8)
Variable	119 (73.9)	111 (68.9)
Poor	1 (0.6)	2 (1.2)
Completers (week 52)	n = 86	n = 80
Good	32 (37.2)	33 (41.2)
Variable	54 (62.8)	47 (58.8)
Poor	0 (0)	0 (0)
Endpoint	n = 130	n = 142
Good	38 (29.2)	45 (31.7)
Variable	88 (67.7)	96 (67.6)
Poor	4 (3.1)	1 (0.7)

[a]PSP ratings of 71 to 100 indicate only mild difficulties, ratings of 31 to 70 indicate varying degrees of disability, and ratings of 0 to 30 indicate functioning so poor that the patient requires intensive support or supervision.
*p < .05 vs. baseline; no significant between-group differences.
Abbreviations: ITT = intention-to-treat, PSP = Personal and Social Performance scale.

point were noted in either group. Mean (SD) changes on the 4-item score were 0.1 (2.2) in the 25-mg group (p = .706) and 0.1 (2.0) in the 50-mg group (p = .573). Mean (SD) changes on the 9-item score were 0.2 (4.8) in the 25-mg group (p = .593) and 0.4 (4.3) for the 50-mg group (p = .226). No significant changes were found on the SQLS for either dose: mean (SD) changes were –1.3 (15.9) in the 25-mg group (p = .372) and –1.0 (15.4) in the 50-mg group (p = .444).

Safety

A total of 289 (89%) of 324 patients had at least 1 treatment-emergent adverse event. The incidence of treatment-emergent adverse events was similar in the 2 treatment groups. The most common adverse events (experienced by ≥ 10% in either treatment group) were insomnia (25-mg dose, 25%; 50-mg dose, 30%), psychotic disorder not otherwise specified (25-mg dose, 23%; 50-mg dose, 18%), headache (25-mg dose, 21%; 50-mg dose, 16%), and anxiety (25-mg dose, 18%; 50-mg, 15%). Overall, 5.9% of patients discontinued treatment due to treatment-emergent adverse events (25-mg dose, 5.5%; 50-mg dose, 6.2%).

Movement disorder–related adverse events were reported in fewer than 10% of patients, with no clinically meaningful differences between doses. Mean ESRS scores decreased over the course of the study for the overall subjective (patient-rated) subscale, the physician's examination for parkinsonism, and the physician's examination for dyskinesia. Baseline-to-endpoint improvements were significant with respect to the physician's examination for parkinsonism for the 25-mg dose, as well as the subjective overall rating and the physician's examination for dyskinesia for the 50-mg dose (Table 7). Other subscale scores (e.g., physician's examinations for akathisia and dystonia) were low (< 1) at baseline and remained so during the study. There were no significant differences between the treatment groups. Similarly, baseline values were low on the AIMS. Mean AIMS scores decreased, but not significantly, in each dose group; there were no significant between-group differences.

Mean (SD) prolactin levels in the 25-mg group were 24.0 (27.5) μg/L at baseline and 33.7 (27.4) μg/L at endpoint (p < .05 from baseline). Corresponding values for the 50-mg group were 25.6 (50.9) μg/L at baseline and 49.6 (44.2) μg/L at endpoint (p < .001 from baseline). Between-group comparisons indicated a significant difference between doses (p < .001). The mean (SD) body weights at baseline were 90.6 (22.9) kg in the 25-mg group and 87.7 (21.9) kg in the 50-mg group. Nonsignificant changes in weight of 0.3 (7.8) kg in the 25-mg group

Table 7. Mean Baseline ESRS Scores and Mean Change From Baseline at Endpoint for Individual ESRS Subscales (safety population)

ESRS Subscale	Possible Range of Scores	Mean (SD) Baseline Score		Mean (SD) Change From Baseline to Endpoint	
		25 mg (n = 163)	50 mg (n = 161)	25 mg (n = 163)	50 mg (n = 161)
Subjective overall rating (items 1–11)	0–33	2.1 (3.0)	2.0 (2.8)	–0.4 (2.7)	–0.5 (2.7)*
Physician's examination for parkinsonism (items 13–30)	0–108	5.0 (6.7)	4.2 (7.4)	–1.4 (4.1)**	–0.9 (6.6)
Physician's examination for dyskinesia (items 51–57)	0–42	1.6 (3.2)	1.5 (3.5)	–0.4 (2.4)	–0.5 (2.5)*

*p < .05; **p < .001.
Abbreviation: ESRS = Extrapyramidal Symptom Rating Scale.

and 1.0 (7.3) kg in the 50-mg group were observed at endpoint. Changes at endpoint in mean glucose, total cholesterol, or triglyceride levels were not significant in either group, nor were there significant between-group differences. The mean (SD) glucose levels were 96.4 (26.5) mg/dL at baseline in the 25-mg group and 98.6 (28.4) mg/dL in the 50-mg group. Mean values at endpoint were 100.5 (33.1) mg/dL and 104.1 (42.0) mg/dL, respectively. The mean total cholesterol levels at baseline were 196.5 (43.9) mg/dL in the 25-mg group and 199.3 (47.6) mg/dL in the 50-mg group. Mean endpoint values were 197.9 (41.1) mg/dL and 194.5 (44.6) mg/dL, respectively. The mean triglyceride levels at baseline were 189.0 (126.9) mg/dL in the 25-mg group and 192.4 (126.2) mg/dL in the 50-mg group. Mean values at endpoint were 195.2 (127.0) mg/dL and 180.5 (121.5) mg/dL, respectively. No significant differences between groups were found with regard to other mean laboratory values.

DISCUSSION

This study examined 1-year outcomes in symptomatically stable patients with schizophrenia or schizoaffective disorder who were transitioned from oral antipsychotics to 1 of 2 doses of long-acting risperidone every 2 weeks. Both doses (25 and 50 mg) of long-acting risperidone were associated with a high proportion of patients who remained out of the hospital (90.1% and 93.8%, respectively) and a high proportion of patients who remained relapse free (78.4% and 85.1%, respectively). Although no statistically significant differences between doses were found on most measures, numeric advantages were noted for the 50-mg group on several endpoints, including median time to relapse and relapse rates. Importantly, the relapse rates in both groups compare favorably to those found by other investigators employing conventional long-acting, conventional oral, or atypical antipsychotics.[1–6,27,28] It should be noted that differences between the population included in our study and populations involved in other studies could also impact relapse rates. Our measure of relapse was determined by broad criteria, including, but not limited to, rehospitalization, while most previous studies have more narrowly defined rehospitalization as the sole measure of relapse. When considering the rate of psychiatric hospitalization in this study (9.9% for the 25-mg group and 6.2% for the 50-mg group) in comparison to others, long-acting risperidone appears to compare favorably. This low rate of hospitalization has a number of implications, not only for an improved course of illness for patients but also for the overall economic burden of schizophrenia.

While no statistically significant difference between groups in the 1-year relapse rate was found, when patients were stratified by prior antipsychotic dose, there were numerical advantages for the 50-mg group. These reached statistical significance in the group of patients who were maintained on average prior doses of antipsychotic before study entry. These latter findings are difficult to interpret, but may suggest that dosage of prior antipsychotic for those patients receiving an average dose may have been affected by limited tolerability. Other unknown factors may confound this finding, such as medication compliance and patient preference. Patients who were receiving a high dose of antipsychotic prior to study entry and were randomly assigned to either the 25- or 50-mg dose of long-acting risperidone had a relapse rate that was relatively higher than expected (26.7% and 21.3%, respectively), suggesting that these patients may be more refractory.

Regardless of randomized dose group, patients demonstrated small, but significant improvement from baseline in PANSS total score and PANSS factor analyses of positive symptoms, negative symptoms, disorganized thought, and anxiety/depression. Similar improvements in clinical status, as measured by the CGI-S, were seen in the 2 treatment groups. Significant improvements in patient functionality, as measured by the PSP, were noted in both treatment groups. These findings suggest that functional improvements can be achieved with continued long-acting risperidone treatment.

Symptomatic and functional improvements occurred in this population of patients who were symptomatically stable at baseline. This observation suggests that continuous delivery of medication can offer additional improvements in patients previously receiving maintenance oral antipsychotic treatment. These data are consistent with re-

sults from a short-term double-blind study[15] and a short-term open-label study,[17] as well as other studies investigating long-term outcomes in similar stable patient populations who were switched to long-acting risperidone injection for 1 year[14] or 6 months.[29] Furthermore, the results of this study reinforce previously published findings that patients can be successfully transitioned from a variety of oral antipsychotics to long-acting risperidone without the need to first transition to oral risperidone.[17,29]

Long-acting risperidone was well tolerated in this study, with no clinically meaningful differences in treatment-emergent adverse events between dose groups. Mean prolactin levels were elevated in both dose groups at baseline and increased significantly at endpoint. The increase was higher in the 50-mg than in the 25-mg dose group, not an unexpected finding for an agent with anti-dopaminergic activity. There was a low incidence of movement disorders reported as adverse events, and patients experienced improvements from baseline to endpoint on the ESRS for the overall subjective (patient-rated) subscale, the physician's examination for parkinsonism, and the physician's examination for dyskinesia, countering clinical lore that long-acting antipsychotics are associated with an increase in extrapyramidal symptoms. Numerical improvement in the AIMS from baseline to endpoint provides additional support for movement disorder improvements. Moreover, these data are consistent with the safety results from an open-label 1-year study of long-acting risperidone.[15]

Several study limitations should be noted. First, relapse rates were lower than anticipated in the power calculation; thus, the study may not have been sufficiently powered to detect a significant difference between the 2 tested doses in the time to relapse in the ITT population. As noted in the Results section, numerical, but not statistically significant, advantages were observed for the 50-mg dose. Second, lack of planned follow-up after relapse does not allow for continued monitoring of patient status over the long term. Furthermore, relapse design studies can lead to higher dropout rates due to the protocol-mandated discontinuation of patients who relapse. In an illness with fluctuating symptomatology, this can limit the availability of potentially useful information. However, the 51% completion rate for this 1-year study provided long-term data on a substantial number of patients (166 non-relapse completers). This study was designed to compare doses of long-acting risperidone; as with any controlled trial, caution must be exercised in drawing comparisons to other trials or populations.

In conclusion, we found low rates of relapse and rehospitalization in this 1-year study of long-acting risperidone injection. Findings suggest that either dose can be considered appropriate. As always, dose selection should be based on patient-specific factors and clinical judgment. Taken together with the results of other studies, our data support the value of maintenance use of long-acting risperidone injection in patients with schizophrenia and schizoaffective disorder for improving long-term symptomatic, functional, and safety outcomes.

Drug names: aripiprazole (Abilify), carbamazepine (Equetro, Carbatrol, and others), chlorpromazine (Thorazine, Sonazine, and others), clozapine (FazaClo, Clozaril, and others), haloperidol (Haldol and others), lorazepam (Ativan and others), loxapine (Loxitane and others), molindone (Moban), olanzapine (Zyprexa), pimozide (Orap), prochlorperazine (Compazine), quetiapine (Seroquel), risperidone (Risperdal), thiothixene (Navane and others), trifluoperazine (Stelazine and others), ziprasidone (Geodon).

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