Safety and Efficacy of Long-Acting Risperidone in Schizophrenia: A 12-Week, Multicenter, Open-Label Study in Stable Patients Switched From Typical and Atypical Oral Antipsychotics

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Background: The safety and efficacy of the first long-acting injectable atypical antipsychotic, risperidone, were assessed in stable patients with schizophrenia switched from oral antipsychotic medications.

Method: Data were collected between July 1, 2001, and October 25, 2002. The study population included patients from clinics, hospitals, and physicians' offices. After a 4-week run-in period, symptomatically stable patients with schizophrenia (DSM-IV) who had been taking haloperidol (N = 46), quetiapine (N = 45), or olanzapine (N = 50) received 25 mg of long-acting risperidone. The oral antipsychotics were continued for 3 weeks after the first injection of long-acting risperidone. Injections were administered every 2 weeks at 25 mg up to a maximum dose of 50 mg for 12 weeks in this multicenter, open-label study.

Results: Long-acting risperidone was well tolerated. Of the 141 patients who participated in the study, the most frequently reported adverse events were insomnia (16%), headache (15%), psychosis (11%), and agitation (11%). The mean increase in body weight was 0.4 kg. No other clinically relevant laboratory abnormalities or significant electrocardiogram changes were observed during the 12-week treatment. Extrapyramidal Symptom Rating Scale total scores were reduced during treatment with long-acting risperidone. Improvements in symptoms of schizophrenia were observed with long-acting risperidone at week 4 and continued through the 12-week treatment with significant reductions in total Positive and Negative Syndrome Scale (PANSS) scores at week 8 (–2.5, $p < .01$) and week 12 (–3.9, $p < .001$). At endpoint, 37% (50/135) of these stable patients were rated as clinically improved (≥ 20% decrease in PANSS total scores).

Conclusions: Switching treatment from oral antipsychotics to long-acting risperidone without an intervening period of oral risperidone was safe and well tolerated. Long-acting risperidone also significantly reduced the severity of symptoms in these stable patients with schizophrenia.

(J Clin Psychiatry 2004;65:1084–1089)

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Dr. Lindenmayer has served as a consultant for Lilly, Pfizer, and Janssen; has received grant/research support from Janssen, Lilly, AstraZeneca, and Repligen; and has participated in speakers or advisory boards for Lilly, Abbott, AstraZeneca, and Bristol-Myers Squibb. Ms. Eerdekens, Dr. Berry, and Dr. Eerdekens are employees of Johnson & Johnson Pharmaceutical R&D.

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Schizophrenia is a chronic illness characterized by a relapsing course and significant morbidity and mortality. Psychotic relapse leads not only to impairment in overall social and occupational function but also to a greater likelihood of poor long-term outcome and prolonged recovery as subsequent episodes occur.[1] Chronic schizophrenia also exacts a heavy economic burden over time, both in direct costs, such as those associated with rehospitalization, emergency room visits, and residential care, and in indirect costs as from loss of productivity and impairment in quality of life of affected persons and their families.[2] The introduction of the atypical antipsychotics has improved outcomes in schizophrenia, but their clinical advantages have often been limited by patients' partial compliance with therapy.[3]

In the treatment of a chronic disease such as schizophrenia, long-acting antipsychotics have several pharmacologic advantages.[4] Their serum concentrations tend to remain consistent and reliable, and their peak and trough levels are not as variable as those seen with oral agents, which often produce adverse effects when peak plasma concentrations are high or when therapy is discontinued abruptly.[4] Long-acting antipsychotics are not associated with first-pass metabolism and can be adjusted more reliably to the lowest effective dose, thereby further reducing the risk of untoward effects. In addition, because these drugs are not self-administered, clinicians can determine

more reliably when patients are suboptimally compliant with therapy. In a meta-analysis of double-blind studies comparing oral and depot antipsychotics in outpatients,[5] long-acting agents were associated with significantly lower relapse rates than were oral agents. These pharmacologic properties have led long-acting antipsychotics to be associated with greater tolerability and efficacy than oral agents.[1,6]

Like other chronic illnesses necessitating long-term treatment, schizophrenia is associated with a significant rate of partial patient compliance with antipsychotic therapy,[7] even with atypical antipsychotics.[3] Partial compliance in patients with schizophrenia can lead to such serious consequences as demoralization, loss of confidence, job loss, family discord, dangerous intentions toward oneself or others, homelessness, more-frequent emergency room visits, and increased risk of relapse and rehospitalization.[1] In a review[8] of 7 studies of patients with schizophrenia, the risk of relapse over a period of 6 months to 2 years was 3.7 times lower among compliant patients. Conversely, compliance with psychotropic therapy was shown to prevent relapse in 90% of patients during a 1-year period versus a 75% relapse rate among patients who received placebo.[9] These findings underscore the need for ongoing treatment with antipsychotic medication in schizophrenia.

The efficacy and safety of long-acting injectable risperidone, the first available long-acting atypical antipsychotic, have been demonstrated in 2 published studies.[10,11] In both studies, patients with schizophrenia or schizoaffective disorder were transitioned to oral risperidone before the initiation of treatment with long-acting risperidone. In the long-term study,[11] 615 symptomatically stable patients, 60% of whom had been receiving oral risperidone, showed substantial improvements when switched to long-acting risperidone. The purpose of the present study was to assess the tolerability and efficacy of long-acting risperidone in clinically stable patients with schizophrenia who were being maintained on oral antipsychotics other than risperidone and who were switched directly to long-acting risperidone without the use of oral risperidone.

METHOD

This was a 12-week, multicenter, exploratory open-label trial of long-acting risperidone in symptomatically stable patients with schizophrenia who were switched from oral treatment with haloperidol, quetiapine, or olanzapine. The study was conducted at 28 sites in the United States. These included 20 clinics, 6 hospitals, and 2 physicians' offices. The study was approved by the institutional review board at each site. Patients' participation in the study was voluntary, and all patients gave written informed consent before enrollment.

Patients were recruited for the study if they met the following inclusion criteria: (1) current treatment with oral haloperidol, quetiapine, or olanzapine for a minimum of 4 months before study entry; (2) DSM-IV criteria for schizophrenia; (3) a maximum baseline Positive and Negative Syndrome Scale[12] (PANSS) total score of 80 and a PANSS score ≤ 4 on each of the following items: conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content; (4) age ≥ 18 years; and (5) a body mass index ≤ 35 kg/m^2 at screening.

Exclusion criteria included a DSM-IV Axis I diagnosis other than schizophrenia (including a history of drug or alcohol dependence within 3 months of screening); unstable or significant medical or neurologic illness (e.g., seizure disorder requiring medication); clinically relevant abnormalities on laboratory test, electrocardiogram (ECG), or physical examination results; history of refractoriness to treatment with risperidone; current antipsychotic treatment at doses exceeding maximum allowed in product labeling; treatment with an investigational drug within the preceding 30 days; serious suicidal ideation or behavior within the last 6 months or significant risk of violent behavior toward others; pregnancy or nursing; and cognitive impairment of sufficient severity to interfere with completion of study assessments. Women of childbearing age without an approved method of birth control were also excluded.

Procedures

Upon meeting study entry criteria and providing written informed consent, subjects entered a run-in period of 4 weeks during which they continued to receive the same dose of their current oral antipsychotic medication and other concomitant psychotropic medication (antidepressants, benzodiazepines, antiparkinsonian agents, mood stabilizers, or hypnotics). All patients received 25 mg of long-acting injectable risperidone at baseline and every 2 weeks during the 12-week study period. According to clinical need and investigator's judgment, the dose of long-acting risperidone could be increased by 12.5-mg increments every 4 weeks (at scheduled visits) to a maximum of 50 mg.

Current oral antipsychotics were continued during the first 2 weeks of long-acting risperidone treatment and then titrated down and discontinued during week 3. Thereafter, if additional antipsychotic medication was required, the patient could receive oral risperidone at the investigator's discretion. Patients also continued to receive their concomitant psychotropic medication at stable pretrial doses (but could continue in study if a dose adjustment was required).

Safety/Efficacy Measures

Safety and tolerability were assessed using clinical observation, self-reports of adverse events (including

Table 1. Baseline Characteristics of the Patients Receiving Long-Acting Risperidone

Characteristic	Prior Antipsychotic Treatment: Haloperidol (N = 46)	Quetiapine (N = 45)	Olanzapine (N = 50)	Total (N = 141)
Sex, % male	57	62	78	66
Age, mean ± SD, y	48.9 ± 14.1	41.7 ± 11.1	44.6 ± 12.2	45.0 ± 12.8
Race/ethnicity, %				
White	41	38	58	46
Black	41	47	26	38
Hispanic	15	11	12	13
Other	2	4	4	4
Schizophrenia diagnosis, %				
Paranoid	48	67	64	60
Undifferentiated	30	24	28	28
Residual	7	7	8	7
Disorganized	15	2	0	6
Age at diagnosis, mean ± SD, y	23.5 ± 6.6	24.4 ± 8.9	25.1 ± 11.3	24.4 ± 9.2

Table 2. Percentage of Patients Who Discontinued the Trial Prematurely and Reasons for Discontinuation

Variable	Prior Antipsychotic Treatment: Haloperidol (N = 46) %	Quetiapine (N = 45) %	Olanzapine (N = 50) %	Total (N = 141) %
Discontinued	22	15	20	19
Adverse event	7	2	2	4
Lack of efficacy	7	4	2	4
Lost to follow-up	2	2	8	4
Withdrew consent	2	7	4	4
Noncompliance	2	0	4	2
Other reasons	2	0	0	1

pain or other reactions at the injection site), standard laboratory tests (including glucose levels), electrocardiography, and physical examination (including weight). Severity of extrapyramidal symptoms (EPS) was evaluated using the 55-item Extrapyramidal Symptom Rating Scale (ESRS).[13] The primary measure of efficacy was the change from baseline to endpoint in PANSS total scores. Secondary outcome measures included the Clinical Global Impressions (CGI) scale[14] to assess overall change in clinical status and the 5 PANSS factors.[15]

Patients were assessed weekly during the first 6 weeks and every 2 weeks for the remaining 6 weeks of the study (or at endpoint for subjects who discontinued treatment prematurely). Safety data were collected at each visit. Patients were rated every 2 weeks with the CGI and every 4 weeks with the PANSS.

Data Analysis

Safety was assessed in all patients who received at least 1 injection of long-acting risperidone, and efficacy was assessed in patients who received at least 1 injection and had a postbaseline PANSS assessment. Descriptive statistics, including patient demographics, clinical characteristics, and incidence of adverse events were summarized for all treated subjects according to initial oral antipsychotic treatment group. Within-group changes from baseline in PANSS and CGI scores were analyzed by paired t tests using observed-case data.

RESULTS

One hundred forty-one patients provided informed consent, completed the run-in period on current oral antipsychotics, and received at least 1 injection of long-acting risperidone. Of these, 135 patients also had at least 1 postbaseline PANSS assessment and were included in the efficacy analysis. The study group was predominately male (66%), with a mean age of 45 years, and 60% had a diagnosis of paranoid schizophrenia (Table 1). Similar numbers of patients were switched from oral antipsychotic treatment with haloperidol (N = 46), quetiapine (N = 45), and olanzapine (N = 50) to long-acting risperidone.

The 12-week trial was completed by 114 patients (81%). Reasons for discontinuation included lack of efficacy (4%), adverse events (4%), lost to follow-up (4%), consent withdrawal (4%), and noncompliance (2%) (Table 2). Of the 6 patients who discontinued because of lack of efficacy, 5 did so after the third injection (i.e., after 4 weeks of treatment with long-acting risperidone).

Dosing and Concomitant Medications

The mean modal (± SD) doses of oral antipsychotics during the run-in period were 13.5 ± 10.4 mg of haloperidol, 398.3 ± 249.6 mg of quetiapine, and 15.4 ± 7.1 mg of olanzapine. Thereafter, of the 141 patients, 52 (37%) received supplementation with oral risperidone tablets (median modal dose = 2 mg; range, 1–6 mg) for a mean duration of 33.4 days. Of the 141 patients, 114 (81%) received all 6 scheduled injections over the 12-week study period. Final doses (injection 6) of long-acting risperidone were 25 mg in 23%, 37.5 mg in 29%, and 50 mg in 48% of patients. In terms of concomitant medications, 40% of patients received sedative-hypnotics, 38% antiparkinsonian agents, 36% antidepressants, 28% analgesics, and 27% anticonvulsants.

Safety and Tolerability

Adverse events reported in ≥ 10% patients in any treatment group are listed in Table 3. These adverse events were generally rated as mild or moderate in intensity. Most frequently reported were insomnia (16%), headache (15%), and psychosis and agitation (11% each). One patient in the prior quetiapine group reported mild pain at the injection site after the first injection of long-acting risperidone. No other injection-site adverse reactions were reported. Five patients (4%) experienced adverse events that led to study discontinuation. Serious adverse events reported in 2 or more patients included

Table 3. Adverse Events Reported in All Patients and in ≥ 10% of Patients in Any Treatment Group

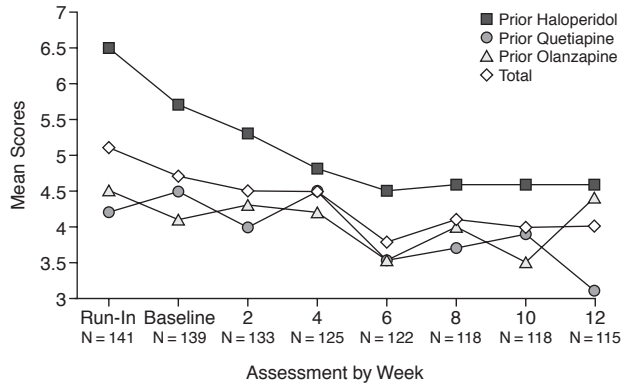
Variable	Prior Antipsychotic Treatment: Haloperidol (N = 46) %	Quetiapine (N = 45) %	Olanzapine (N = 50) %	Total (N = 141) %
Any adverse event	83	84	76	81
Insomnia	11	18	20	16
Headache	11	29	6	15
Psychosis	17	9	8	11
Agitation	9	18	6	11
Anxiety	7	16	4	9
Rhinitis	9	7	10	9
Diarrhea	13	9	2	8
Hyperprolactinemia	4	11	6	7
Pain	11	4	2	6
Abdominal pain	2	11	0	4

Table 4. Mean (± SE) PANSS Total Scores and Positive and Negative Factor Scores at Baseline, and Mean Changes at Endpoint of Treatment With Long-Acting Risperidone

Variable	Prior Antipsychotic Treatment: Haloperidol (N = 44)	Quetiapine (N = 43)	Olanzapine (N = 48)	Total (N = 135)
PANSS total				
Baseline	62.3 ± 1.8	62.0 ± 1.8	60.4 ± 1.7	61.5 ± 1.0
Change at endpoint	–1.2 ± 0.5	–2.0 ± 0.6	–2.6 ± 0.7	–1.9 ± 0.6
Positive symptoms				
Baseline	18.2 ± 0.6	19.3 ± 0.7	18.2 ± 0.6	18.5 ± 0.4
Change at endpoint	–0.7 ± 0.6	–1.3 ± 0.6*	–1.3 ± 0.7	–1.1 ± 0.4
Negative symptoms				
Baseline	15.3 ± 0.7	14.2 ± 0.6	14.9 ± 0.7	14.8 ± 0.4
Change at endpoint	0.1 ± 0.6	–0.6 ± 0.6	–1.0 ± 0.6	–0.5 ± 0.4

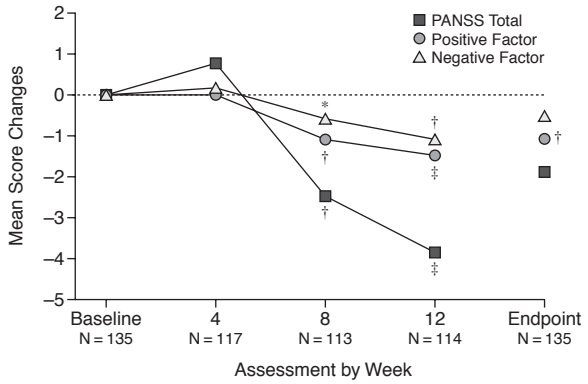
*p < .05 vs. baseline.
Abbreviaton: PANSS = Positive and Negative Syndrome Scale.

Figure 1. ESRS Total Scores From Start of the Run-In Period to Week 12 in Prior Haloperidol, Quetiapine, and Olanzapine Groups and in Total Patients



Abbreviation: ESRS = Extrapyramidal Symptom Rating Scale.

Figure 2. Mean Changes From Baseline in PANSS Total Scores and Scores on the Positive and Negative Symptom Factors



*p < .05 vs. baseline.
†p < .01 vs. baseline.
‡p < .001 vs. baseline.
Abbreviation: PANSS = Positive and Negative Syndrome Scale.

psychosis in 9 patients (6%) and agitation in 3 (2%) and were considered by the investigator to be related to chronic schizophrenia rather than to the drug. No deaths were reported during treatment with long-acting risperidone.

EPS-related adverse events were spontaneously reported by 11 (8%) patients, including 7 (15%) in the prior haloperidol group and 2 (4%) in each of the prior quetiapine and olanzapine groups. Severity of EPS was low at run-in and tended to become even less severe in each of the groups during treatment with long-acting risperidone (Figure 1). The mean increase in body weight at endpoint was 0.4 kg in the total group. Mean weight gain was 1.4 kg in the prior haloperidol group and 0.3 kg in the prior quetiapine group, while patients who had received olanzapine experienced a mean weight loss of 0.5 kg.

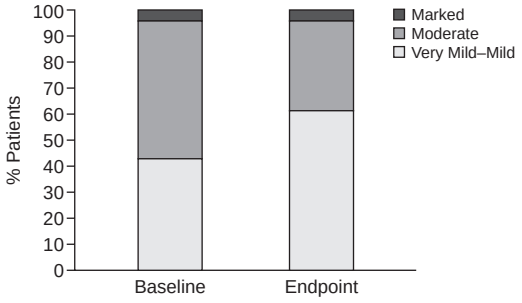
Both glucose and triglyceride levels were reduced from baseline to endpoint in each of the patient groups (mean glucose levels from 6.2 to 5.8 mmol/L and mean triglyceride levels from 2.3 to 2.0 mmol/L in the total group).

Hyperprolactinemia was reported in 10 patients, and 1 patient reported dysmenorrhea. Dysmenorrhea was judged as not being related to treatment. Mean (± SE) serum prolactin concentrations were 23.5 ± 2.4 ng/mL at baseline and 52.2 ± 3.7 ng/mL at endpoint. No other clinically relevant laboratory abnormalities or significant ECG changes, including QTc prolongation, were reported during the 12-week treatment.

Efficacy

Overall symptom improvements (PANSS total scores) were seen in each of the 3 patient groups during treatment with long-acting risperidone (Table 4). In the total group, improvements from baseline were significant at week 8 ($p < .01$) and week 12 ($p < .001$) (Figure 2). PANSS positive factor scores improved from baseline to endpoint in all 3 patient groups, and negative factor scores improved in the prior quetiapine and prior olanzapine groups; the

Figure 3. Percentages of Patients (N = 135) Whose Illness Was Rated as Very Mild to Mild, Moderate, and Marked at Baseline and Endpoint[a]



[a]Clinical Global Impressions-Severity scores.

changes were significant ($p < .05$) only for the positive factor in the prior quetiapine group (Table 4). No or minimal changes were noted on the 3 PANSS factors of disorganized thoughts, hostility/excitement, and depression/anxiety. Fifty patients (37%) were rated as clinically improved (≥ 20% reduction in PANSS total scores) at endpoint.

Illness severity (CGI-severity scores) was judged to be very mild to mild in 43% of the patients at baseline and in 61% at endpoint (Figure 3). Mean CGI-severity scores were reduced in each patient group during treatment: –0.3 in both the prior haloperidol and quetiapine groups ($p < .05$) and –0.1 in the prior olanzapine group.

DISCUSSION

Long-acting risperidone was safe and well tolerated: over 80% of patients completed the 12-weeks of treatment, and only 5 discontinued treatment because of adverse events. Adverse effects, which can have a negative impact on compliance, were reported infrequently and were generally mild. Of particular relevance were the low incidence of EPS-related adverse events (reported in only 8% of patients) and reduction in the severity of EPS (ESRS total scores) throughout the study period in these stable patients. Only 1 patient reported an adverse event related to the injection site: mild pain at the time of the first injection of long-acting risperidone. Injection site reactions are commonly reported with long-acting conventional agents[16,17] and may be due to their oil-based formulations. Long-acting risperidone is a water-based formulation.

According to admission criteria, only patients judged to be clinically stable at baseline could be considered for study participation. At baseline, mean PANSS total scores ranged from 60.4 to 62.3 in the 3 patient groups, and in most patients (96%), illness severity at baseline was judged to be very mild to moderate according to the CGI-severity scale. Despite this low symptom rating, mean PANSS total scores improved in each patient group. Of significance was the finding of clinical improvement (≥ 20% reduction in PANSS total scores) in 37% of the patients at endpoint. These results indicate that long-acting risperidone can have added clinical effectiveness in patients who are already considered symptomatically stable while receiving typical or atypical oral antipsychotics.

The results suggest that switching stable patients from oral antipsychotic medication to the new atypical long-acting formulation is a clinically appropriate and a beneficial treatment option resulting in further symptomatic improvement. The results also indicate that patients stable on their current oral antipsychotic medication can be safely switched to long-acting risperidone while being maintained on their oral antipsychotic for a further 3 weeks. ESRS scores were reduced from the run-in period to endpoint, particularly in the prior haloperidol group, and no changes were noted on any of the other safety measures.

Although all patients were started at 25 mg of long-acting risperidone at baseline, in close to half of them (48%) the dose was gradually increased from a baseline dose of 25 mg by 12.5-mg increments at 4-week intervals, not to exceed 50 mg at endpoint. A flexible-dose approach often results in a tendency to increase the dose if clinical effects are not immediately seen, and most often does not lead to dose reductions if no side effects are reported. This hypothesis was investigated in a post hoc analysis in which we examined whether increases in the dose of long-acting risperidone were related to an increase in symptom severity (PANSS and CGI scores) or appearance of a psychiatric adverse event. Of the 152 dose increases during the study, 82 (54%) were not associated with a documented symptom exacerbation or appearance of a psychiatric adverse event. These results indicate that in many cases lack of effect or clinical worsening was not the reason for increasing the dose.

Although 40% of patients received concomitant psychotropics or oral risperidone, the use of these medications is unlikely to have influenced the outcome of the trial. The use of oral risperidone increased from 0.7% of patients on day 14 to 16.6% on day 28 and 26.3% on day 42, and decreased thereafter to 24.6% on day 56, 20.4% on day 70, and 16.3% on day 84. We examined this issue further in a post hoc analysis by comparing the group without oral risperidone and the group with oral risperidone during the period of 3 weeks after the first injection to week 12. PANSS total scores were 60.8 at baseline and 55.6 at week 12 in the group without oral supplementation and 61.4 and 60.2, respectively, in the group with oral risperidone. PANSS scores were reduced in both groups from baseline to endpoint, although the reduction was lower in the group that had received oral supplementa-

tion, again pointing to the possibility that patients with a lesser response tended to receive higher antipsychotic doses.

The double-blind, randomized, fixed-dose study by Kane et al.[10] showed that the 25-mg and 50-mg doses of long-acting risperidone were overall equivalent. The proportions of patients who reached the clinical threshold of improvement were 47% in the 25-mg group, 48% in the 50-mg group, and only 39% in the 75-mg group. Patients in the 25-mg group, however, required no more antiparkinsonian medication than the placebo group, while the 50-mg and the 75-mg groups required significantly more. The Fleischhacker et al. study[11] was a flexible-dose, open-label study in which the 3 doses (25, 50, and 75 mg) of long-acting risperidone were based on the dose of the preceding antipsychotic. As expected, patients in the 75-mg group were less responsive than patients in the 25-mg and 50-mg groups. More patients in the 75-mg group than in the other 2 groups discontinued treatment because of insufficient response. In the same study, antiparkinsonian medications were received by 23% of the 25-mg group, 34% of the 50-mg group, and 37% of the 75-mg group. Taken together, these comparisons, while not all based on double-blind data, would favor the 25-mg dose as the preferred dose in terms of both efficacy and tolerability.

Among the major limitations of this study are its open-label design and the lack of a comparator. This meant that raters were nonblind to the treatments and could have been biased. However, the primary goal of the study was to examine the safety of long-acting risperidone, while its efficacy has been established in published studies.[10,11] Other limitations are the flexible-dose approach and the fact that psychotropic concomitant medications (including oral risperidone) were allowed during the trial. On the other hand, these characteristics may allow for a closer approximation to the natural setting and for greater clinical generalizability of our results.

CONCLUSIONS

Stable patients with schizophrenia can be safely transitioned to long-acting risperidone from oral antipsychotics such as haloperidol, quetiapine, and olanzapine. The switch to long-acting risperidone also reduced the severity of symptoms in these symptomatically stable patients.

Drug names: haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal).

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