Neuropsychopharmacology (2010) 35, 2367–2377

www.neuropsychopharmacology.org

Relapse Prevention in Schizophrenia and Schizoaffective Disorder with Risperidone Long-Acting Injectable *vs* Quetiapine: Results of a Long-Term, Open-Label, Randomized Clinical Trial

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Chronic management of schizophrenia and schizoaffective disorders is frequently complicated by symptomatic relapse. An open-label, randomized, active-controlled, 2-year trial evaluated 710 patients with schizophrenia or related disorders who were switched from stable treatment with oral risperidone, olanzapine, or conventional neuroleptics to risperidone long-acting injectable (RLAI) or oral quetiapine. Primary effectiveness evaluation was time-to-relapse. Safety evaluations included adverse events (AEs) reported for the duration of the study, Extrapyramidal Symptom Rating Scale (ESRS), clinical laboratory tests, and vital signs. A total of 666 patients ($n = 329$ RLAI, $n = 337$ quetiapine) were evaluable for effectiveness measures. Baseline demographics were similar between treatment groups. Kaplan–Meier estimate of time-to-relapse was significantly longer with RLAI ($p < 0.0001$). Relapse occurred in 16.5% of patients with RLAI and 31.3% with quetiapine. RLAI and quetiapine were both safe and well tolerated. Weight gain affected 7% of patients with RLAI and 6% with quetiapine, with mean end point increases of 1.25 ± 6.61 and 0 ± 6.55 kg, respectively. There were no significant between-group differences in weight gain. ESRS total scores decreased similarly after randomization to either RLAI or quetiapine. Extrapyramidal AEs occurred in 10% of patients with RLAI and 6% with quetiapine. Treatment-emergent potentially prolactin-related AEs were reported in 15 (5%) patients with RLAI and 5 (2%) patients with quetiapine; hyperprolactinemia was reported in 43 (13.1%) patients with RLAI and 5 (1.5%) patients with quetiapine. Somnolence occurred in 2% of patients with RLAI and 11% with quetiapine. To our knowledge, this is the first report of a randomized clinical trial directly comparing relapse prevention with a second-generation long-acting injectable antipsychotic and oral therapy. Time-to-relapse in stable patients with schizophrenia or schizoaffective disorder was significantly longer in patients randomized to RLAI compared with those randomized to oral quetiapine. Both antipsychotics were generally well tolerated.
Neuropsychopharmacology (2010) **35,** 2367–2377; doi:10.1038/npp.2010.111; published online 4 August 2010

Keywords: risperidone; quetiapine; relapse prevention; schizophrenia; long-acting injectable; schizoaffective disorder

INTRODUCTION

Medication adherence is a major challenge in the clinical care of patients with schizophrenia. During the first month of therapy, 60–85% of patients with schizophrenia are adherent, with only 50% adherent by the sixth month of treatment (Llorca, 2008). Poor treatment tolerability is a main contributor to antipsychotic nonadherence or partial adherence (Yamada *et al*, 2006), which may be addressed by choosing efficacious medications with favorable tolerability profiles, such as atypical antipsychotics. Other factors contributing to nonadherence and partial adherence include lack of insight, health beliefs, problems with treatment access, embarrassment/stigma over illness, patient or family opposed to medications, no perceived daily benefit, medication interferes with life goals, poor therapeutic alliance, complicated treatment regimen, cognitive dysfunction, and lack of social support (Dolder *et al*, 2002; Löffler *et al*, 2003; Kane, 2007; Linden and Godemann, 2007).

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Received 24 November 2009; revised 15 June 2010; accepted 16 June 2010

Poorer insight and increased conceptual disorganization have been independently associated with nonadherence (Acosta *et al*, 2009). Medication formulation can also affect adherence, with more reliable administration assured using depot formulations, which may result in improved long-term symptomatic control maintenance (Kane, 2006; Leucht and Heres, 2006).

Non- or partial treatment adherence is a major risk factor for relapse and rehospitalization of patients with schizophrenia (Leucht and Heres, 2006). A review of studies comparing 1-year relapse with oral *vs* depot antipsychotics reported substantially more relapse with oral therapy (42 *vs* 27%) (Schooler, 2003). To date, two long-acting injectable atypical antipsychotics have been developed and undergone randomized controlled clinical trials for the treatment of schizophrenia: risperidone long-acting injectable (RLAI) and olanzapine pamoate. RLAI is approved and available in Europe and the United States. Approval of olanzapine pamoate in the United States has been delayed because of safety concerns; however, the European Commission approved it in November 2008, with labeling requiring 3 h of observation in a health-care facility by appropriately qualified personnel after each administration for the occurrence of postinjection delirium sedation syndrome (severe sedation occurring after about 1% of olanzapine pamoate injections (Citrome, 2009)).

Long-term relapse data with long-acting injectable atypical antipsychotics are available for RLAI. Comparison of long-term benefit with RLAI and oral risperidone has been evaluated in several studies. In a 2-year naturalistic study, 55 consecutive patients were prospectively treated with open-label RLAI or oral risperidone (Kim *et al*, 2008). Compliance was significantly better with RLAI *vs* oral risperidone at both 1 year (86 *vs* 54%, $p<0.01$) and 2 years (81 *vs* 55%, $p<0.01$). Relapse was significantly less frequent with RLAI at 1 year (18 *vs* 50%, $p=0.03$) and 2 years (23 *vs* 75%, $p<0.01$). A recent *post hoc* analysis of studies treating adults with schizophrenia and lifetime treatment with antipsychotic for $\leqslant 12$ weeks compared 2-year efficacy with open-label RLAI ($n=50$) with double-blind treatment with oral risperidone or haloperidol ($n=47$) (Emsley *et al*, 2008). Among treatment responders, relapse occurred in significantly fewer patients treated with RLAI *vs* oral antipsychotics (9.3 *vs* 42.1%, $p=0.001$). Relapse was also indirectly evaluated using hospitalization as a marker in the observational electronic Schizophrenia Treatment Adherence Registry (Olivares *et al*, 2009b). Patients initiated on RLAI ($n=1345$) or a new oral antipsychotic ($n=277$) were monitored for 2 years. The most common oral atypicals initiated were risperidone (35.7%) and olanzapine (36.5%). Treatment retention at 2 years was 82% with RLAI and 63% with oral antipsychotics ($p<0.0001$). Hospitalization had occurred during the 12 months before RLAI in 35% of patients, decreasing to 14% during the first year of RLAI and 8% during the second year. Hospitalization had occurred during the 12 months before oral antipsychotic for 27 *vs* 10% of patients during the first year after initiating oral antipsychotic and 9% during the second year. Benefits from RLAI may be because of better achievement of steady-state drug levels with long-acting injectable therapy, better treatment adherence, increased contact with health-care providers to receive injections, and other factors.

This study was designed to expand on data from earlier studies, by investigating whether RLAI would provide better effectiveness maintenance over 2 years compared with oral quetiapine, when used in routine care settings of general psychiatric services. The primary effectiveness parameter was time-to-relapse. To our knowledge, this is the first published report directly comparing relapse prevention in a randomized, controlled study treating patients with a long-acting injectable *vs* oral second-generation antipsychotic. This study was conducted in an open-label manner because of ethical concerns involved with blinding already approved oral and injectable therapies for long-term treatment. This study was not designed to determine factors that might influence differences in relapse between a long-acting injectable *vs* daily oral therapy. The use of nonblinded treatment in this study allows a more real-world evaluation of treatment effectiveness, which will be influenced by adherence, rather than a direct efficacy analysis of differences in the pharmacological agents risperidone and quetiapine.

MATERIALS

This multicenter, open-label, randomized, active-control, long-term treatment with RLAI *vs* oral quetiapine was conducted from October 2004 to November 2007 at 124 sites (see Appendix) in 25 countries (ClinicalTrials.gov identifier: NCT00216476). Results of a small descriptive arm with patients also randomized to aripiprazole will be described separately. This additional analysis with aripiprazole was included in the trial because aripiprazole was a relatively new drug at the time the study was designed and aripiprazole has been shown to have a favorable safety and tolerability profile compared with other atypical antipsychotics, including relatively low risks for weight gain and metabolic dysfunction (Pae, 2009). This trial was conducted in accordance with guidelines of the International Conference on Harmonization for Good Clinical Practice. The study protocol and consent were approved by ethic committees/institutional review boards. Informed consent was obtained on all patient candidates before enrollment.

Patients

Symptomatically stable adults aged $\geqslant 18$ years were eligible if they met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria (American Psychiatric Association, 1994) for schizophrenia or schizoaffective disorder, and were candidates for switching therapy because of insufficient symptomatic control, side effects, or patient request. Candidates were considered symptomatically stable when using a stable dose of antipsychotic for $\geqslant 4$ weeks (including monotherapy with oral risperidone $\leqslant 6$ mg daily, olanzapine $\leqslant 20$ mg daily, or a conventional neuroleptic $\leqslant 10$ mg haloperidol or its equivalent) and were living in the same residence for $\geqslant 30$ days. Women were surgically sterile or practicing effective contraception with a baseline negative pregnancy test. Patients were excluded if they were previously determined to be nonresponders to risperidone, quetiapine, or $\geqslant 2$ antipsychotics despite adequate drug plasma levels

(previous nonresponders because of nonadherence were not excluded); had a DSM-IV axis I diagnosis other than schizophrenia or schizoaffective disorder; were treated with antipsychotics other than oral risperidone, olanzapine, or conventional oral neuroleptics or with mood stabilizers or antidepressants and had not received a stable dose for $\geqslant 3$ months before study entry; had phenylketonuria or hypersensitivity to risperidone or quetiapine; had drug or alcohol dependence during the preceding 1 month; or were at acute risk or had a history of suicide attempt(s).

Treatment

Treatment recommendations followed approved dosing guidelines for both drugs. Stratified randomization according to previous treatment used three strata: oral risperidone (40%), olanzapine (30%), and conventional oral neuroleptics (30%). Patients were randomly allocated 1 : 1 to RLAI or quetiapine, or alternatively in countries where aripiprazole was available 2 : 2 : 1 to RLAI, quetiapine, or aripiprazole, respectively. As noted above, results for those patients randomized to aripiprazole will be described in a separate publication. Eligible patients were randomly assigned to open-label RLAI or oral quetiapine for up to 24 months. During titration and throughout the study, nursing assessments occurred every 2 weeks (at the time of RLAI injection or over the phone for patients randomized to quetiapine). If a patient's psychotic condition had a negative change, an unscheduled additional visit was made.

RLAI was initiated with 25 mg injections every 2 weeks, with patients continuing current oral medication (risperidone, olanzapine, or neuroleptic) for the first 3 weeks of RLAI treatment before tapering off baseline oral antipsychotic over 1–2 weeks. Risperidone-naive patients randomized to RLAI received 2 mg oral risperidone daily for 2 days before the first RLAI injection to ensure tolerability. RLAI dosage could be increased by 12.5 mg for worsening of psychotic symptoms or insufficient effectiveness to the maximum approved dose of 50 mg every 2 weeks. Increases were only permitted during scheduled visits and at $\geqslant 4$ weeks after a previous dose change. RLAI dosage could be decreased as needed because of adverse events (AEs).

Quetiapine was initiated at 25 mg twice daily, with patients given a titration schedule for increasing quetiapine by 25–50 mg two- to three-times daily on the second and third day, as tolerated, to achieve a target dosage by day 4 of 300–400 mg daily in divided doses, two- to three-times daily. If needed, additional dosage adjustments of 25–50 mg per day were permitted at $\geqslant 2$ days to the maximum approved daily dose of 750 mg. Antipsychotics used before randomization were tapered off over 2 weeks, starting after the first administration of quetiapine.

Mood stabilizers or antidepressants used in stable doses for $\geqslant 3$ months before enrollment were continued after enrollment. Changes in dosage or initiation of a mood stabilizer or antidepressant were permitted during this study, if clinically necessary. Permitted concomitant medications included anticholinergics and benzotropine mesylate for extrapyramidal symptoms, benzodiazepines for sleep, and β-blockers for hypertension or treatment-emergent akathisia.

Assessments

Patient demographics, disease characteristics, a physical examination, and serum prolactin levels were obtained at an initial screening visit. Weight, height, and questionnaires assessing symptom severity were obtained at a subsequent baseline evaluation 2 weeks later. Assessments occurred every 2 weeks (with injection for patients treated with RLAI and by phone for quetiapine) for changes in patient status necessitating an unscheduled visit. Follow-up appointments were conducted every 3 months. Symptom severity measures were obtained at each visit, including the Positive and Negative Syndrome Scale (PANSS) and change in Clinical Global Impression (CGI)-Severity. Vital signs were recorded at treatment months 3 and 6, and then every 6 months. Weight was evaluated every 6 months, with body mass index (BMI) calculated using baseline height. Urinalysis and serum tests of hematology, chemistries, and prolactin were obtained annually. Extrapyramidal symptoms were evaluated using the Extrapyramidal Symptom Rating Scale (ESRS) (Chouinard *et al*, 1980), a valid measure of drug-induced movement disorders that effectively discriminates drug-induced disorders from psychiatric symptoms (Chouinard and Margolese, 2005). ESRS measures four types of drug-induced movement disorders (parkinsonism, akathisia, dystonia, and tardive dyskinesia) and was obtained at baseline and treatment months 3, 6, 12, 18, and 24.

The primary effectiveness assessment was the time from randomization to documentation of relapse, defined using criteria from a previous risperidone comparative study (Csernansky *et al*, 2002):

- psychiatric hospitalization
- increase in level of care necessary and $\geqslant 25\%$ increase in PANSS total score from baseline or increase of 10 points when baseline score was $\leqslant 40$
- deliberate self-injury
- emergence of clinically significant suicidal or homicidal ideation
- violent behavior resulting in significant injury to another person or property
- significant clinical deterioration defined as a CGI–Change score of 6 (much worse)
- exceeding registered drug dose (50 mg/2 weeks for RLAI and 750 mg daily for quetiapine)

Relapsed patients were required to meet any of the criteria above on two consecutive evaluations, 3–5 days apart, with the first visit considered the time of relapse. Effectiveness was also evaluated by mean changes in total PANSS.

Safety and tolerability were assessed by recording treatment-emergent AEs at each visit. AEs were considered to be serious if they resulted in: hospitalization or prolongation of existing hospitalization, significant or persistent disability, life-threatening symptoms or death, or a condition judged to be clinically significant by the investigator. Clinically significant changes in clinical laboratory tests, ESRS score, weight, and BMI were also evaluated.

Data Analysis

Using data from studies comparing 1-year relapse with depot *vs* oral antipsychotics (27 *vs* 42% relapse over 1 year) (Schooler, 2003), this study assumed a relapse rate of 0.30 with RLAI and 0.42 with quetiapine. A sample size of 251 patients per treatment was calculated as needed to detect, with 80% power, a 0.05 level two-sided difference in equality of survival curves, by means of log-rank test. To adjust for an estimated 20% patient discontinuation for reasons other than relapse, we determined a minimum of 628 patients to be necessary.

Based on protocol design, an analysis of effectiveness was performed after the last patient had completed 1 treatment year. The protocol allowed early trial termination if the last patient completed 1 year of follow-up and a difference in effectiveness at the 0.1% significance level (two-tailed) was observed.

All patients treated with at least one dose of study drug were eligible for effectiveness and tolerability analyses (intent-to-treat). Relapse rate was analyzed using the Kaplan–Meier method. The primary comparison of time-to-relapse between RLAI and quetiapine was performed using the log-rank test with α, adjusted for the planned analysis after the last patient had completed 1 year of treatment, to ensure an overall α level of 5%. A hazard ratio was calculated to estimate the difference in relapse risk between RLAI and quetiapine. Mean time-to-relapse was estimated with the Kaplan–Meier product limit method, in which nonrelapsed dropouts are accounted for by decreasing the number at risk at the relapse event following the dropout, and not by their actual observation time. Therefore, the Kaplan–Meier estimate of time-to-relapse differs from the mean observed time of patients and, if there are many dropouts, can be higher than the mean treatment duration. The significance level for end-point testing of the primary parameter, time-to-relapse, was set to 3% ($\alpha = 3\%$ and confidence interval (CI) = 97%) to ensure an overall significance level of 5% when tested initially in an interim analysis and subsequently for the final analysis that is reported in this paper.

Demographics, disease characteristics, and AEs were assessed using descriptive analyses. Percentage change in PANSS was determined as (follow-up PANSS−baseline PANSS)/baseline PANSS. For secondary parameters, observed case analysis was applied. The end point, that is the last observation, was created using the last observation carried forward method. Within-group differences for ordinal/continuous data were assessed using the Wilcoxon two-sample test. Nominal data were tested using the Fisher exact test. All statistical tests were interpreted at the 5% significance level (two-tailed). Safety differences between treatments were not statistically tested because the study was not powered to show differences or equivalence in these parameters.

RESULTS

The results of the prespecified analysis after the last patient had completed 1 year of treatment led to the recommendation by independent experts to terminate the trial early due to achieving the predetermined difference in effectiveness.

Patients

A total of 710 patients were enrolled and randomized to RLAI ($n = 355$) or quetiapine ($n = 355$) (Figure 1).

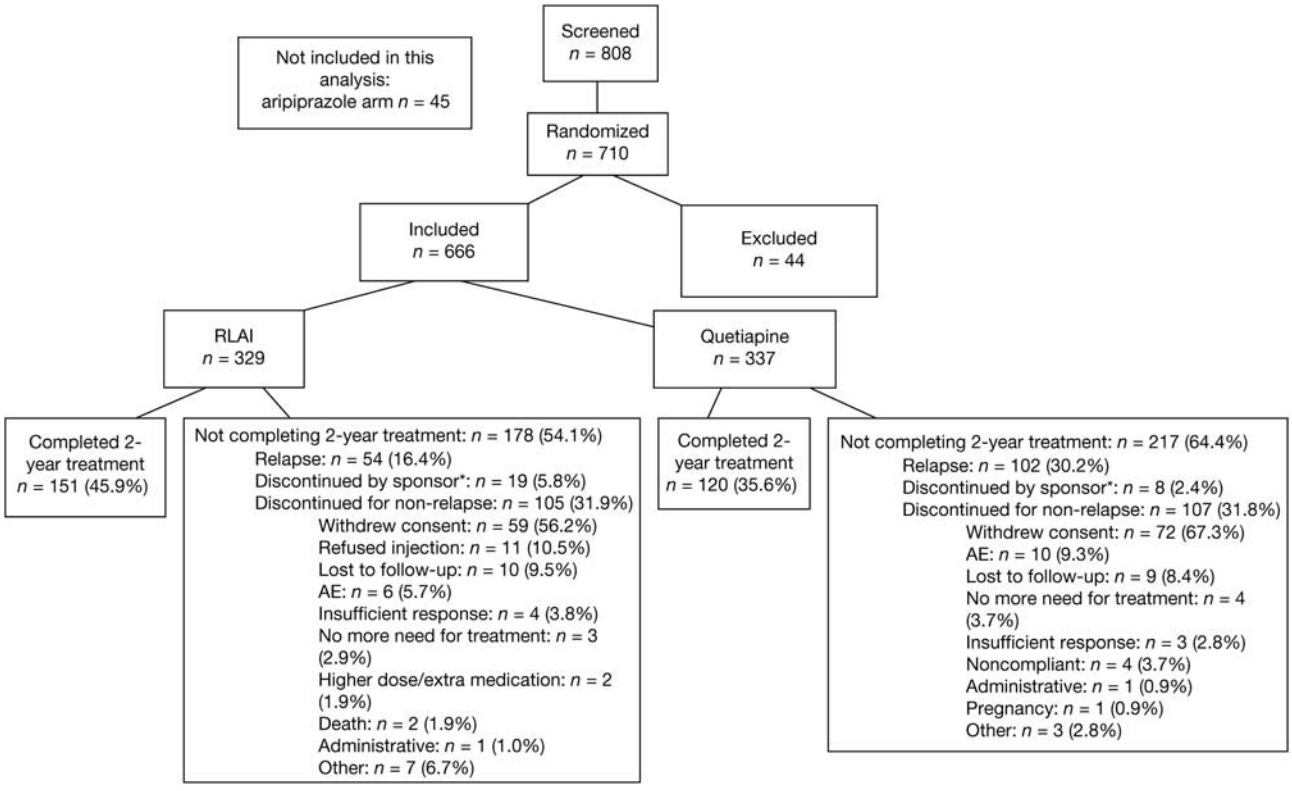

Figure 1 Patient disposition. AE, adverse event; RLAI, risperidone long-acting injectable. *Treatment discontinued because of the study being stopped early by the sponsor because the prespecified analysis showed that the predetermined difference in effectiveness had been achieved.

Data collected on 25 patients from one site were excluded from effectiveness and safety analyses because the study at that site was not conducted in a manner consistent with Good Clinical Practice Guidelines. An additional 19 patients (14 RLAI, 5 quetiapine) did not receive trial medication, leaving an evaluable data set of 666 patients. As intended per stratification, 49% of the patients ($n = 328$) included in the study used oral risperidone as antipsychotic therapy before the study, 22% ($n = 144$) were on olanzapine, and 29% ($n = 194$) were on conventional oral neuroleptic monotherapy. A total of 19 patients treated with RLAI and 8 with quetiapine were ongoing at the time the study was stopped per the prespecified analysis by the sponsor. Baseline demographics were similar between treatment groups (Table 1). Mean baseline PANSS score of 73 in both groups corresponded to being moderately ill (Leucht *et al*, 2005). Patients were permitted to endorse >1 reason for discontinuing or switching treatment, with similar reasons endorsed by those patients randomized to RLAI or quetiapine. Reasons for switching included insufficient effectiveness with persistent negative symptoms in 30.5% of patients, positive symptoms in 13.7%, general symptoms in 21.8%, and AEs in 17.1%. Among patients randomized to RLAI, 49.8% had previously used oral risperidone; among patients randomized to quetiapine, 48.7% had previously used oral risperidone. As noted previously, patients who had been identified as nonresponders to either risperidone or quetiapine were excluded from this study; therefore, although about half of the patients in each group had been previously treated with oral risperidone or quetiapine, none of the included patients was considered to be a nonresponder.

Table 1 Baseline Demographics

Characteristic	RLAI ($n = 329$)	Quetiapine ($n = 337$)
Mean ± SD age (years)	40.6 ± 12.5	42.6 ± 13.1
Gender, n (%)		
Male	195 (59.3)	191 (56.7)
Female	134 (40.7)	146 (43.3)
Diagnosis, n (%)		
Schizophrenia	273 (83.0)	275 (81.6)
Schizoaffective disorder	56 (17.0)	62 (18.4)
Mean ± SD time since symptom diagnosis (years)	9.9 ± 9.9	10.0 ± 10.1
Mean ± SD number of psychiatric hospitalizations	5.0 ± 6.5	5.5 ± 7.3
Symptom severity, mean ± SD score		
PANSS	72.7 ± 21.0	73.2 ± 22.2
CGI-S	2.8 ± 1.0	2.7 ± 1.0
ESRS	4.2 ± 6.7	4.2 ± 7.0

Abbreviations: CGI-S, Clinical Global Impression-Severity; ESRS, Extrapyramidal Symptom Rating Scale; PANSS, Positive and Negative Syndrome Scale; RLAI, risperidone long-acting injectable; SD, standard deviation.

Two-year treatment was completed by 151 (45.9%) patients randomized to RLAI and 120 (35.6%) to quetiapine ($p = 0.0074$). Excluding patients who discontinued because of relapse, no differences were observed in other reasons for discontinuation between the treatment groups. The most common reasons for discontinuation included withdrawal of consent (33.4%), AEs (4.6%), lost to follow-up (4.8%), and refused injection (2.8%). The most common reasons for discontinuation in nonrelapsed patients included withdrawal of consent (61.8%), AEs (7.5%), and lost to follow-up (9.0%). Mean duration of treatment was 483.8 ± 277.8 days with RLAI and 400.7 ± 290.6 days with quetiapine. The mode drug doses were 33.6 ± 10.1 mg every 2 weeks with RLAI and 413.4 ± 159.2 mg daily with quetiapine.

Concomitant medications were used by 82.7% with RLAI ($N = 272$) and 75.1% with quetiapine ($N = 253$). Concomitant medications most commonly used by patients treated with RLAI and quetiapine, respectively, were lorazepam (14.6 and 10.1%), diazepam (12.8 and 14.2%), and biperiden (12.5 and 11.3%). Concomitant medications most frequently started during the course of treatment with RLAI and quetiapine, respectively, were diazepam (8.5 and 9.8%), lorazepam (8.5 and 5.9%), and paracetamol (6.4 and 4.5%). Antidepressants were used by 22.8% of patients treated with RLAI and 22.3% treated with quetiapine.

Effectiveness

Effectiveness data were available for 327 patients treated with RLAI and 326 with quetiapine. A Kaplan–Meier plot was generated for time to confirmed relapse, the primary end point (Figure 2). A log-rank test for equality of survival distributions between treatments showed a significant difference in time-to-relapse for patients treated with RLAI *vs* quetiapine ($p < 0.0001$). The 25th quartile of time-to-relapse for quetiapine was 248.0 days (97% CI = 205.0–397.0

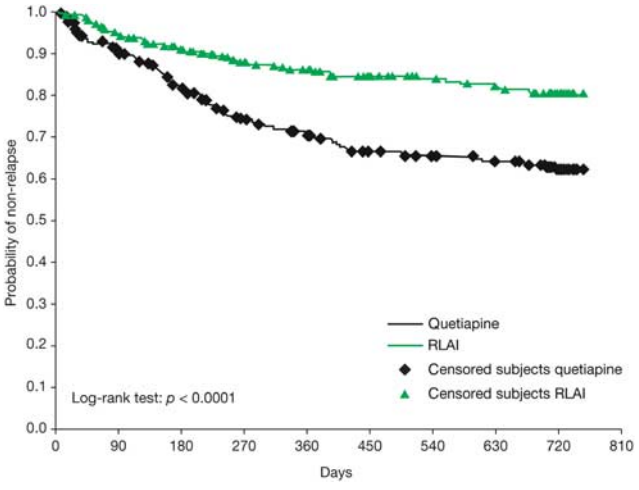

Figure 2 Kaplan–Meier estimate of relapse-free time. Among 327 subjects treated with risperidone long-acting injectable (RLAI), relapse occurred in 54; among the 326 subjects treated with quetiapine, relapse occurred in 102. Censored subjects are those not relapsing by the time of assessment.

days). This quartile could not be defined for RLAI as the percentage of RLAI-treated patients experiencing relapse was <25%. The relative risk for relapse was less than half with RLAI compared with quetiapine (hazard ratio = 0.46, 97% CI = 0.32–0.67). At the excluded site, 13 patients were treated with quetiapine and 12 with RLAI. There were two relapses, one in each treatment arm. Analysis on the primary parameter, with and without these patients, did not reveal any statistical difference. Relapse occurred in 54 of 327 patients (16.5%) treated with RLAI and 102 of 326 patients (31.3%) with quetiapine. Reported reasons for relapse are in Table 2. More than one reason was permitted, with only 32 patients (20.5%) reporting a single reason.

A subanalysis was performed among patients treated with RLAI to determine if pretrial use of oral risperidone affected effectiveness outcome. Before enrollment, 163 patients were treated with oral risperidone and 164 were treated with other antipsychotics. During RLAI treatment, 27 patients in each group relapsed. There was no difference in time-to-relapse between the two previous-medication groups (255.3 ± 231.12 days in patients previously using oral risperidone *vs* 234.4 ± 206.4 days in patients using other antipsychotics). The Kaplan–Meier estimate of the mean relapse-free period was 607.9 ± 16.3 days for patients using oral risperidone immediately before switching to RLAI *vs* 598.2 ± 16.0 days for those using other antipsychotics.

Improvements in mean PANSS total scores are shown in Table 3. Baseline and end-point data were available for 326 patients treated with RLAI and 325 with quetiapine. Total PANSS improved significantly compared with baseline for both groups at each posttreatment assessment ($p<0.001$). Numerical improvements at end point reached statistical significance for RLAI ($p<0.001$), but not for quetiapine ($p=0.10$). A significant difference was seen between RLAI and quetiapine at treatment months 15, 21, and 24 ($p<0.05$), and at end point ($p<0.001$). At end point, PANSS improvement was ⩾20% for 42% of RLAI and 30% of quetiapine patients, ⩾30% for 30% of RLAI and 17% of quetiapine patients, ⩾40% for 15% of RLAI and 7% of quetiapine patients, and ⩾50% for 7% of RLAI and 3% of quetiapine patients ($p<0.05$).

Table 2 Reasons for Relapse, *n* (%)

Reason	RLAI (*n* = 54)	Quetiapine (*n* = 102)
Clinical deterioration	41 (75.9)	80 (78.4)
Increased care plus 25% increased PANSS score	33 (61.1)	69 (67.6)
Psychiatric hospitalization	33 (61.1)	54 (52.9)
Requiring a dose higher than the approved dose	10 (18.5)	22 (21.6)
Suicidal/homicidal ideation	8 (14.8)	4 (3.9)
Violent behavior	6 (11.1)	12 (11.8)
Self-injury	5 (9.3)	2 (2.0)

Abbreviations: PANSS, Positive and Negative Syndrome Scale; RLAI, risperidone long-acting injectable.

Safety and Tolerability

Changes in vital signs, urinalysis, and serum hematology and chemistry tests with both groups were small. The incidence of treatment-emergent AEs was similar between groups (Table 4). The most common serious AEs were psychiatric symptoms (15% with RLAI and 18% with quetiapine). Death occurred in three patients treated with RLAI (one deep vein thrombosis with peptic ulcer perforation and two suicides) and two with quetiapine (myocardial infarction and suicide). None of the deaths was considered

Table 4 Treatment-Emergent AEs, *n* (%)

AE	RLAI (*n* = 329)	Quetiapine (*n* = 337)
Any AE	225 (68.4)	235 (69.7)
Serious AE	63 (19.1)	77 (22.8)
Common AEs		
Psychiatric symptoms	142 (43.2)	145 (43.0)
Prolactin-related	45 (13.7)	11 (3.3)
Weight gain	23 (7.0)	21 (6.2)
Headache	20 (6.1)	17 (5.0)
Somnolence	6 (1.8)	38 (11.3)
Relationship to study drug		
None/doubtful	222 (67.5)	186 (55.2)
Possible/probable/very likely	107 (32.5)	151 (44.8)
Extrapyramidal symptom AEs		
Any	34 (10.3)	19 (5.6)
Tremor	10 (3.0)	2 (0.6)
Dystonia	1 (0.3)	2 (0.6)
Hyperkinesia	13 (4.0)	8 (2.4)
Parkinsonism	15 (4.6)	6 (1.8)
Dyskinesia	1 (0.3)	3 (0.9)

Abbreviations: AE, adverse event; RLAI, risperidone long-acting injectable.

Table 3 Mean PANSS Total Scores (*n*)

Treatment group	Treatment month										
	Baseline	1	3	6	9	12	15	18	21	24	End point
RLAI (*n*)	72.7 (326)	68.7 (325)	65.8 (298)	61.7 (268)	58.6 (240)	56.8 (220)	54.9 (198)	53.8 (189)	53.1 (180)	50.9 (173)	63.4 (326)
Quetiapine (*n*)	73.2 (325)	70.4 (319)	66.0 (284)	65.9 (249)	64.5 (210)	62.2 (181)	60.3 (160)	58.8 (146)	58.2 (139)	56.9 (131)	72.1 (325)

Abbreviation: PANSS, Positive and Negative Syndrome Scale.

Table 5 Patients with Reported Prolactin-Related AEs at End Point According to Gender

	RLAI ($n=329$)		Quetiapine ($n=337$)	
	Female ($n=134$)	**Male ($n=195$)**	**Female ($n=146$)**	**Male ($n=191$)**
Potentially prolactin-related, *n* (%)	10 (7.5)	5 (2.6)	5 (3.4)	0
Hyperprolactinemia, *n* (%)	27 (20.1)	16 (8.2)	4 (2.7)	1 (0.5)
	($n=107$)	**($n=145$)**	**($n=104$)**	**($n=133$)**
Mean ± SD prolactin levels (mIU/l)	1590.5 ± 924.57	767.4 ± 540.68	855.1 ± 1066.92	367.0 ± 352.51

Abbreviations: AE, adverse event; RLAI, risperidone long-acting injectable.
Bold values: analysis not designed to test for differences.

to be related to the study drug. Somnolence was reported in 2% of RLAI-treated and 11% of quetiapine-treated patients. Extrapyramidal symptom AEs occurred more often with RLAI *vs* quetiapine (10.3 *vs* 5.6%), with parkinsonism the most commonly reported individual extrapyramidal symptom AE (4.6 *vs* 1.8%). Treatment-emergent potentially prolactin-related AEs were reported in 15 patients with RLAI (4.6%) and 5 with quetiapine (1.5%). The percentage of patients discontinuing the study because of prolactin-related AEs was low for both drugs; 0.3% for quetiapine and 1.8% for RLAI. Hyperprolactinemia, that is elevated prolactin plasma levels based on laboratory testing, occurred in 43 patients with RLAI (13.1%) and 5 with quetiapine (1.5%). The percentage of female patients reporting potentially prolactin-related AEs was 7.5% with RLAI and 3.4% with quetiapine. Hyperprolactinemia in females occurred in 20.1% with RLAI and 2.7% with quetiapine. In male patients, potentially prolactin-related AEs were only reported with RLAI (2.6%) and not with quetiapine. The percentage of male patients reporting hyperprolactinemia was 8.2% with RLAI and 0.5% with quetiapine. Similarly, the mean prolactin levels at end point were lower for quetiapine compared with RLAI for both genders (Table 5).

Weight gain was reported in 23 patients (7.0%) treated with RLAI and 21 (6.2%) with quetiapine. Mean weight change at end point was 1.25 ± 6.61 kg with RLAI and 0 ± 6.55 kg with quetiapine. There were no significant between-group differences. Among those patients who completed 2 years of treatment, mean increase in weight from baseline to 24 months was 1.16 ± 7.11 kg with RLAI and 0.84 ± 7.51 kg with quetiapine. Mean BMI increases from baseline to end point were small and not significantly different between treatment groups (0.3 ± 2.38 kg/m^2 with RLAI *vs* 0.3 ± 2.59 kg/m^2 with quetiapine).

Decreases in ESRS compared with baseline were significant at each assessment and end point for both RLAI and quetiapine ($p<0.001$). There were no significant between-group differences. Mean end-point total ESRS scores were 1.90 ± 4.31 with RLAI and 2.07 ± 4.51 with quetiapine, resulting in end-point changes *vs* baseline of -2.32 ± 4.56 with RLAI and -2.07 ± 4.67 with quetiapine.

DISCUSSION

Time-to-relapse in patients with clinically stable schizophrenia or schizoaffective disorder treated with oral risperidone, olanzapine, or a typical antipsychotic was significantly longer when switched to treatment with RLAI compared with oral quetiapine ($p<0.0001$). Patients switched to RLAI were also less likely to experience symptom relapse. Over 2 years of possible treatment in this study, twice as many patients treated with quetiapine relapsed compared with RLAI (31% with quetiapine *vs* 17% with RLAI). The benefit for RLAI treatment over quetiapine emerged early and was sustained up to 2 years.

Relapse in this study with RLAI compared favorably with relapse rates reported in earlier studies. Data from this study expand on data available in previously published long-term studies by using a larger sample size than some of the previously published comparative studies (Kim *et al*, 2008; Emsley *et al*, 2008) and providing a direct comparison against quetiapine. Because of nonblinded treatment with oral *vs* injectable therapy used in this study and the ability to more completely ensure compliance with injectable therapy, this study provides more insight into the differences between two treatment approaches rather than a direct comparison of two pharmacological agents. These data are important because they reflect more real-world use of therapy, where adherence is better ensured with injectable therapy. This study, however, did not include a detailed analysis of medication adherence, which might have added additional useful information.

End-point improvements in PANSS similarly favored RLAI. Interestingly, between-group differences seemed to become apparent after 6 months of treatment, when treatment adherence has been shown for only half of patients prescribed antipsychotics (Llorca, 2008). This study did not evaluate adherence directly, but this may be interesting to evaluate in future studies to identify the role of medication adherence *vs* benefits related to the drug itself. Applying criteria from a recent comparison of PANSS and CGI scores (Leucht *et al*, 2005) to the results of this study showed illness severity at baseline suggested moderate illness for both treatment arms, whereas end-point improvement in PANSS corresponded to a reduction to nearly-mild illness severity with RLAI only.

Approved doses based on the Summary of Product Characteristics were selected for both drugs and mean doses of both drugs were similar to effective doses reported in other controlled clinical trials. The dose of quetiapine used in this study may have been lower than doses used for some patients in clinical practice. A recent review of the

dose–response relationship of quetiapine in schizophrenia concluded that optimal dosage of quetiapine is 150–800 mg per day, with most data supporting an optimal dosage of about 300–400 mg per day; some data, however, do support that higher doses of 600–800 mg per day may be more advantageous (Sparshatt *et al*, 2008). Doses used in this study, however, were comparable to other published data. For example, a double-blind comparison of oral risperidone, quetiapine, or placebo in adults with schizophrenia with an acute exacerbation requiring hospitalization used a target quetiapine dose of 400–600 mg per day, with a maximum of 600–800 mg per day (Potkin *et al*, 2006). The mean modal dose at treatment day 42 was 556.4 ± 141.9 mg per day. In addition, a recent review of health care claims database dosing information reported an average overall daily initiation dose with quetiapine of 358.83 mg and an end dose of 382.56 mg for patients with schizophrenia (Citrome *et al*, 2009).

Overall tolerability was generally similar with both treatments and comparable to previously published studies (Schooler, 2003; Gharabawi *et al*, 2007). Most treatment-emergent AEs were transient and did not result in any change in therapy. Serious AEs were reported for 19% of patients treated with RLAI, compared with 27% from an earlier trial switching stable patients to 1-year, open-label treatment with RLAI (Gharabawi *et al*, 2007). Weight gain affected 7% of patients treated with RLAI and 6% with quetiapine, with a mean increase at 24 months of 1.16 ± 7.11 kg with RLAI and 0.84 ± 7.51 kg with quetiapine. At end point, mean weight increase was 1.25 ± 6.61 kg with RLAI and 0 ± 6.55 kg with quetiapine. Extrapyramidal AEs occurred for 10% with RLAI and 6% with quetiapine. ESRS total scores decreased similarly after switching to either RLAI or quetiapine. Potentially prolactin-related AEs occurred more frequently with RLAI, and hyperprolactinemia occurred in 43 patients with RLAI (13%) and 5 with quetiapine (2%). Previous studies have reported a lower risk of hyperprolactinemia for patients treated with quetiapine (Emsley *et al*, 2008; Taylor, 2009; Madhusoodanan *et al*, 2010). In this study, potentially prolactin-related AEs and incidence of hyperprolactinemia were lower with quetiapine. These prolactin-related findings may pose a limitation for RLAI in both male and female patients, although discontinuation rates because of potentially prolactin-related AEs were low for both drugs (1.8% with RLAI and 0.3% with quetiapine). Somnolence occurred more frequently with quetiapine (11 *vs* 2%) similar to previous observations (Harvey *et al*, 2007; Said *et al*, 2008).

This study additionally highlights the difficulty of achieving long-term treatment persistence in patients with schizophrenia, even when involved in a controlled study. Over half of all patients in this study withdrew before completing the full 2-year treatment; however, rates and reasons for withdrawal were similar between assigned treatments. Rates and reasons for withdrawal were also comparable to an earlier, analogous study of stable patients with schizophrenia or schizoaffective disorder randomized to oral risperidone or haloperidol, with 18% of patients given either risperidone or haloperidol withdrawing because of patient choice, and 12% with risperidone and 15% with haloperidol withdrawing because of side effects; withdrawal for reasons other than relapse occurred in 14% with risperidone and 20% with haloperidol (Csernansky *et al*, 2002). Similarly, only 12 of the initial 29 patients in a trial randomizing patients to quetiapine or haloperidol decanoate for 48 weeks completed treatment (Glick and Marder, 2005).

To our knowledge, this is the first published report comparing relapse prevention with a long-acting injectable *vs* oral atypical antipsychotic, using relapse prevention as the primary efficacy assessment. Additional strengths of this study are the inclusion of a substantial female cohort and the long duration of follow-up. As determined through a prespecified data analysis after the last patient completed 1 year of follow-up, this trial was terminated early because a difference in effectiveness at the 0.1% significance level had already been achieved. Because of this early study termination, treatment was discontinued in 19 patients treated with RLAI and 8 with quetiapine before completing the full 2-year treatment.

Interpretation of data from this study is limited by those factors inherent to open-label treatment studies. A double-blind design requiring patients to accept placebo injections over a 2-year period for treatment with drugs in an approved indication, however, would have been unethical. Similar to previously published studies evaluating long-term outcome with RLAI *vs* oral therapy, this study does not differentiate benefit due to risperidone *vs* benefit due to the injectable formulation. Previous studies comparing effectiveness with RLAI and oral antipsychotics similarly showed reduced relapse with RLAI; however, treatment adherence is generally better with RLAI, which likely confers a substantial impact to better effectiveness maintenance (Kim *et al*, 2008; Emsley *et al*, 2008; Olivares *et al*, 2009a). These data suggest that adherence and effectiveness maintenance are better with RLAI, similar to the report of this study. Furthermore, this study excluded previously determined nonresponders to risperidone, quetiapine, or $\geqslant 2$ antipsychotics; therefore, results achieved in this study may be better than those found when treating general clinical or treatment-naive patients. Finally, health-care provider contact was greater with RLAI, because of the need for repeated injections; in an effort to equalize health-care provider contact, patients randomized to quetiapine received an equivalent number of follow-up contacts, although these occurred through telephone. Although the impact of contacts is likely greater with face-to-face interactions for the RLAI group, this difference does more closely simulate what would occur in routine clinical practice follow-up for patients receiving RLAI *vs* an oral antipsychotic therapy. It is important to recognize, however, that some of the benefit from RLAI in this study may have been related to the increased health-care provider contact time necessary for patients receiving an injectable therapy. This study was not designed to determine factors that might influence differences in relapse between a long-acting injectable *vs* daily oral therapy. Future studies may wish to evaluate possible predictive factors. In addition, although medication adherence was generally ensured in this study, a detailed evaluation of treatment adherence was not conducted and such information might be useful to include in future research.

In this study, as patients were clinically stable but requiring/desiring a treatment change at study entry,

additional analysis on extent of improvement would supplement data on evaluation of symptom worsening or relapse after switching therapies. Future analyses may include an evaluation of factors that may have predicted relapse in each patient group, including treatment noncompliance, baseline remission, and baseline symptom severity. In addition, patients taking oral risperidone as maintenance therapy immediately before switching to RLAI may have responded differently than those using a different antipsychotic, because of pre-RLAI initiation receptor binding from oral risperidone and possibly previously showed effectiveness and tolerability to a risperidone formulation. Subsequent analyses of benefits with RLAI may wish to include a comparison based on pretreatment antipsychotic use. Finally, the effect of diagnosis was not evaluated in this study, although the distribution of diagnoses was similar in both treatment arms. Future analyses of these data may wish to include a comparison of outcome based on a diagnosis of schizophrenia *vs* schizoaffective disorder.

In summary, data from this study support earlier studies showing good relapse prevention in stable patients with schizophrenia or schizoaffective disorder switched to treatment with RLAI. Relapse was significantly lower among patients using RLAI compared with those using oral quetiapine. Both RLAI and quetiapine were safe and well tolerated.

ACKNOWLEDGEMENTS

This study was sponsored by Janssen-Cilag Medical Affairs EMEA. We thank Rossella Medori for trial design and medical conduct supervision. Dr Medori was European Medical Director at Janssen-Cilag during study conduct and analysis. We also thank Robert Wapenaar from Janssen-Cilag, the Netherlands, for providing statistical analyses. Editorial support was provided by Remon van den Broek and team from Excerpta Medica.

DISCLOSURE

W Gaebel has received research grants from, and served as consultant, advisor, and speaker for AstraZeneca, Janssen-Cilag, Eli Lilly, Servier, Lundbeck, and Wyeth Pharma; A Schreiner is a full employee of Janssen-Cilag, Medical Affairs EMEA, Germany; P Bergmans is a full employee of Janssen-Cilag, Medical Affairs, Clinical Research Information Group, the Netherlands; R de Arce has received research grants from, and served as consultant, advisor, or speaker for AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Janssen-Cilag, Novartis, Bristol, Pfizer, sanofi-aventis, and UCB Pharma; F Rouillon has received grants from, and served as consultant, advisor, and speaker for Bristol-Myers Squibb, sanofi-aventis, Servier, Lundbeck, Eli Lilly, Wyeth, and Biocodex; J Cordes has received grants from, and served as a consultant, advisor, and speaker for Pfizer, Lundbeck, AstraZeneca, Eli Lilly, Janssen-Cilag, Bristol-Myers Squibb, Alpine Biomed, and Servier; L Eriksson served as consultant, advisor, and speaker for Janssen-Cilag, AstraZeneca, Eli Lilly, and Bristol-Myers Squibb; E Smeraldi served as consultant, advisor, and speaker for Janssen-Cilag, InnovaPharma, and Wyeth.

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