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Double-Blind Comparison of Olanzapine Versus Risperidone in the Treatment of Schizophrenia and Other Psychotic Disorders

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Olanzapine and risperidone, both second-generation antipsychotic agents, represent two different pharmacologic strategies. Although they share some *in vitro* properties, they differ by virtue of their chemical structure, spectrum of receptor binding affinities, animal neuropharmacology, pharmacokinetics, and *in vivo* neuroimaging profile. Based on such differences, it was hypothesized that the two compounds would show distinct safety and/or efficacy characteristics. To test this hypothesis, an international, multicenter, double-blind, parallel-group, 28-week prospective study was conducted with 339 patients who met DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder. Results of the study indicated that both olanzapine and risperidone were safe and effective in the management of psychotic symptoms. However, olanzapine demonstrated significantly greater efficacy in negative symptoms (Scale for Assessment of Negative Symptoms summary score), as well as overall response rate (≥40% decrease in the Positive and Negative Syndrome Scale total score). Furthermore, a statistically significantly greater proportion of the olanzapine-treated than risperidone-treated patients maintained their response at 28 weeks based on Kaplan-Meier survival curves. The incidence of extrapyramidal side effects, hyperprolactinemia, and sexual dysfunction was statistically significantly lower in olanzapine-treated than risperidone-treated patients. In addition, statistically significantly fewer adverse events were reported by olanzapine-treated patients than by their risperidone-treated counterparts. Thus, the differential preclinical profiles of these two drugs were also evident in a controlled, clinical investigation. Olanzapine seemed to have a risk-versus-benefit advantage. (J Clin Psychopharmacol 1997;17:407–418)

SCHIZOPHRENIA, THE MOST SEVERE of the mental disorders, is frequently characterized by a chronic recurrent course. With conventional antipsychotic agents, at least 30% of schizophrenic patients exhibit an inadequate or poor response.[1] Moreover, as many as 60% experience relapse after 1 year of therapy.[2] Further complicating management of the schizophrenic patient is an estimated rate of noncompliance between 11% and 80%.[3] In part, noncompliance, which may include early discontinuation of medication against medical advice, is attributable to the high incidence of drug-related side effects, especially extrapyramidal symptoms (EPS).[4] Each of these factors contributes to a pattern of repeated hospital admissions and progressive social and occupational dysfunction.

Since the introduction of clozapine, the search for "atypical" or "novel" antipsychotic agents has led to a variety of investigational compounds exhibiting different pharmacologic profiles. Although without consensus, evidence of a low EPS risk within a therapeutic range has been a common defining criterion of "atypicality."[5] Other criteria often include a broader efficacy profile than conventional agents (e.g., in treating negative symptoms) and minimal perturbation of the dopamine-sensitive hormone prolactin.[6]

Both risperidone and olanzapine exhibit greater serotonin ($5\text{-}HT_{2A}$) than dopamine (D_2) antagonism.[7,8] Clinical studies have shown that both drugs are effective in the control of psychotic symptoms, including both positive symptoms[9–14] and negative symptoms.[9–15] Although both share these similarities, they differ in their chemical structure, profile of receptor binding affinities, animal neuropharmacology, pharmacokinetics, and

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TABLE 1. Relative receptor affinities of olanzapine and risperidone[a]

Receptor	Affinity: Olanzapine	Affinity: Risperidone	Reference No.
D_1	++	++	8
D_2	+++	++++	8
D_4	+++	++++	8
5-HT_{2A}	++++	++++	8
5-HT_{2C}	+++	+++	8
5-HT_3	++	—	8
5-HT_6	++++	+	16
5-HT_7	+	++++	16
α_1	+++	++++	8
α_2	+	++++	8
H_1	++++	+	8
M_1	++++	—	8
M_2	+++	—	8
M_3	+++	—	8
M_4	+++	—	8

[a]Relative potencies are based on a comparison of published K_i values for these agents. The symbol + denotes a K_i value of 100 to 200; the symbol ++ denotes a K_i value of 30 to 99; the symbol +++ denotes a K_i value of 10 to 29; the symbol ++++ denotes a K_i value of 0.5 to 9; the symbol — denotes inhibition of binding <50% at 10,000 nM concentration. D, dopamine; 5-HT, 5-hydroxytryptamine; α, alpha-adrenergic, H, histamine; M, muscarinic.

relative striatal D_2 displacement in human imaging studies (Tables 1 and 2).[8,16-25]

Based on these preclinical and clinical differences, it was hypothesized that olanzapine would differentiate from risperidone *in vivo* on features of safety or efficacy or both. To test this hypothesis, a prospective, double-blind, parallel group, controlled, international, multicenter, 28-week study was conducted in a sample of 339 patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder.

Subjects and Methods

Study design

The study was conducted by 38 investigators in nine countries (Belgium, France, Germany, The Netherlands, South Africa, Spain, Switzerland, the United Kingdom, and the United States). Thirty-five investigators randomized at least one patient per treatment arm with at least one third of the total patients assigned to one of the treatment arms at all 35 investigational sites. The study protocol was approved by each site's institutional or ethical review board, and a signed, informed consent was obtained from all eligible patients after the procedures and possible side effects were explained. The study consisted of three study periods: (1) a washout period from previous antipsychotic drugs (2 to 9 days for oral antipsychotic drugs; at least one injection cycle for depot antipsychotics); (2) a 28-week double-blind therapy period in which patients were randomly allocated in a 1:1 ratio to treatment with olanzapine 10 to 20 mg/day or risperidone 4 to 12 mg/day for 28 weeks; and (3) an optional double-blind 1- to 6-day end-of-study medication taper period. Data are presented here for the 28-week double-blind study period. No analysis of the taper period was planned or conducted; 45 olanzapine-treated and 39 risperidone-treated patients entered the taper period.

Patients started olanzapine therapy at 15 mg/day once daily for the first 7 study days. Thereafter, investigators could adjust the daily olanzapine dosage upward or downward by 5 mg every 7 days (range 10–20 mg). Consistent with risperidone labeling, patients began risperidone titration at a dosage of 1 mg twice daily on day 1, 2 mg twice daily on day 2, and then 3 mg twice daily on days 3 through 7. After the first week, investigators could adjust the daily risperidone dosage

TABLE 2. Comparison of *in vivo* neuropharmacology of olanzapine and risperidone[a]

Activity/Effect	Olanzapine	Risperidone	Reference No.
Paw test (ratio of dose increasing forelimb vs. hindlimb reaction time)	20	10	17
Selective reversal of PCP-induced social withdrawal (social isolation)	Yes	No	18
Chronic administration does not decrease nigrostriatal dopaminergic neuronal activity	Yes	U-shaped dose response	19
Increases responding in rat conflict model	Yes	No	20
Conditioned avoidance (CAR) vs. catalepsy (CAT) (ratio = CAT [ED50]/CAR [ED50])	8.4	7.0	21
Antagonism of PCP-induced deficits in prepulse inhibition	Yes	?	22
Striatal D_2 occupancy (SPET)	Low, =clozapine	High, >clozapine, =typical agents	23
C-fos expression selectively activated in the nucleus accumbens	Yes	Yes	24, 25

[a]CAR, conditioned avoidance response; CAT, catalepsy; D, dopamine; PCP, phencyclidine; SPET, single photon emission tomography; ED50, dose required to produce a 50% maximal cataleptic response (CAT) or a 50% block of the avoidance response (CAR).

upward or downward by 2 mg/day (1 mg two times daily) every 7 days within the approved range of 4 to 12 mg/day. With both drugs, titration was permitted to optimize an individual patient's outcome. Concomitant psychotropic medications were not allowed during the study with the exception of limited benzodiazepine or chloral hydrate use for agitation and insomnia and biperiden or benztropine mesylate (up to 6 mg/day) for treatment-emergent EPS. Prophylactic use of anticholinergic medications was prohibited.

Subjects

Patients were men or women between the ages of 18 and 65 who met DSM-IV criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder and exhibited a minimum score on the Brief Psychiatric Rating Scale (BPRS) extracted from the Positive and Negative Syndrome Scale (PANSS)[26] of at least 42 (items scored 1 to 7). Patients could begin the study as inpatients or outpatients, and a change in hospitalization status during participation in the protocol was permissible. No comorbid or other recent major axis I disorder was allowed. Pregnant or lactating women or patients with serious medical illnesses in which pharmacotherapy posed a substantial clinical risk or confounded diagnosis were excluded. In addition, patients were excluded if they had failed to show at least minimal clinical response with at least three antipsychotics in three chemical classes dosed at ≥800 chlorpromazine equivalents per day or clozapine dosed at ≥400 mg/day for at least 6 weeks.

Assessment

Clinical assessments were carried out at the screening visit followed by a baseline assessment after the washout period. Postrandomization follow-up assessments were conducted weekly during the first 8 weeks of double-blind therapy and every 4 weeks thereafter, except as noted below.

At the screening visit, a standard history, physical examination, and laboratory profile were obtained. Serum prolactin was measured at baseline (immediately before starting double-blind treatment), at the end of 8 weeks of therapy, at the first dose decrease because of an adverse event, and at discontinuation or completion of double-blind therapy. An electrocardiogram (ECG) was performed at the screening visit and after 4, 8, and 28 weeks of double-blind therapy or at early discontinuation.

The efficacy measures included the PANSS total (primary efficacy measure) and its subscales (positive, negative, general psychopathology); the PANSS depression item; the 18-item BPRS total extracted from the PANSS; the Clinical Global Impressions—Severity of Illness Scale (CGI-S),[27] and the Scale for the Assessment of Negative Symptoms (SANS).[28] The BPRS was analyzed on a scale of 0 to 108 by subtracting 1 from each of the 18 items. Videotapes of patient interviews produced by the authors of the scale were used to train investigators in the use of the PANSS at study initiation. Interrater reliability was not assessed.

Adverse events were detected by clinical evaluation and spontaneous report at each visit and mapped, classified, and recorded using a system based on the U.S. Food and Drug Administration Coding Symbols and Thesaurus for Adverse Reaction Terms (COSTART).[29] In addition, adverse events were solicited by the investigative site using the 40-item Association for Methodology and Documentation in Psychiatry (AMDP-5) adverse event questionnaire.[30, 31] The questionnaire was administered at baseline, after 1 and 4 weeks of double-blind therapy, and every 4 weeks thereafter. EPS, akathisia, and dyskinesia were further assessed with the Simpson-Angus Scale,[32] the Barnes Akathisia Scale,[33] and the Abnormal Involuntary Movement Scale (AIMS).[34] The patients' quality of life was assessed with the Quality of Life Scale,[35] whereas the economic burden of illness was estimated by periodic evaluation of patients' healthcare resource utilization.

The modal study drug dose for an individual patient was defined as the most frequently administered daily dosage of study drug for that patient. Patients were considered to be compliant with the study drug if the daily dosage taken, as assessed by tablet count and patient report, was within 80% to 120% of the prescribed dose at all visits.

Statistical methods

The primary intent of this study was to evaluate the effectiveness and safety of olanzapine versus risperidone during double-blind therapy. A one-sided lower 95% confidence interval for the difference in last observation carried forward (LOCF) mean change in PANSS total score for risperidone minus olanzapine was used in the primary efficacy analysis to determine whether olanzapine was equivalent or superior to risperidone. The inference was based on the lower bound of the confidence interval. A lower bound >0 indicated that olanzapine was statistically significantly superior to risperidone. A lower bound ≥ -4 and ≤ 0 indicated there was no difference between the two treatments. A lower bound < -4 indicated no conclusion could be drawn regarding the superiority of olanzapine compared with risperidone.

All endpoint analyses used an LOCF algorithm; that is, the last available visit (visits 3 through 15, weeks 1 through 28) served as endpoint. For analyses of baseline efficacy and safety measures and change from baseline to endpoint, only patients with a baseline (visit 2, week 0) and at least one postbaseline measure were included. In the computation of total scores, if any of the

individual items were missing, then the total score was treated as missing. For the categorical analysis of decreases in laboratory analyte values, only patients whose baseline laboratory values were at or above the lower limit of the reference range were included in the analysis. For the categorical analysis of increases in laboratory analyte values, only patients whose baseline values were at or below the upper limit of the reference range were included in the analysis.

An analysis of variance (ANOVA) model with terms for treatment, geographic region, and treatment-by-geographic region interaction was used to evaluate continuous data. Both original and rank-transformed data were fit to the ANOVA models evaluating LOCF change from baseline to endpoint in the efficacy and safety measures; the primary inference was taken from the analysis of the original data unless the assumptions of the ANOVA seemed to be violated. Least-squares means were used to calculate between-treatment group p values. The Wilcoxon signed-rank test was used to test the hypothesis that within-treatment group change from baseline to endpoint was significant.

For the LOCF analysis of change in PANSS total score, the change from baseline was evaluated at each visit for all patients. The ANOVA model used did not include the treatment-by-geographic region interaction term because of potentially sparse data.

Categorical data (demographic variables, anticholinergic use, response rates, compliance, reasons for study discontinuation, treatment-emergent adverse events, treatment-emergent EPS, and laboratory analytes) were evaluated using Pearson's χ^2 test. Response rates (LOCF) were evaluated for patients who achieved reductions in PANSS total scores of 20%, 30%, 40%, and 50% from baseline to endpoint, as specified in the study protocol.

The incidence of treatment-emergent EPS based on adverse events was assessed by grouping events into five categories: (1) dystonic events (dystonia, generalized spasm, neck rigidity, oculogyric crisis, opisthotonos, torticollis); (2) parkinsonian events (akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, masked facies, tremor); (3) akathisia events (akathisia, hyperkinesia); (4) dyskinetic events (buccoglossal syndrome, choreoathetosis, dyskinesia, tardive dyskinesia); and (5) residual events (movement disorder, myoclonus, twitching). If a patient experienced one or more extrapyramidal adverse events that mapped to one of these five categories, the patient was counted once in that category. If a patient experienced an extrapyramidal adverse event that mapped to more than one category, the patient was counted once in each applicable category. Because some patients could be counted more than once with this tabulation system, an additional category ("any extrapyramidal event") showing the proportion of patients who experienced at least one extrapyramidal adverse event (thus counted only once) was also included.

The incidence of EPS based on rating scales was evaluated as follows. To assess treatment-associated pseudoparkinsonism, the proportion of patients with a Simpson-Angus scale total score >3 at any postbaseline visit was calculated among those with a total score ≤3 at baseline. To assess treatment-associated akathisia, the proportion of patients with a Barnes Akathisia Scale global score ≥2 at any postbaseline visit was calculated among those with a score <2 at baseline. To assess treatment-associated abnormal dyskinetic movements, the proportion of patients with a score of ≥3 on any one of the AIMS items 1 through 7 or a score of ≥2 on any two of the AIMS items 1 through 7 at any postbaseline visit was calculated among those without either of these criteria at baseline. The latter definition is consistent with the cross-sectional research diagnostic criteria suggested by Schooler and Kane.[36]

A survival analysis was performed to estimate time maintaining response (time not exhibiting a significant symptom exacerbation after achieving response criteria at 8 weeks) at 12 weeks and 28 weeks of therapy. A significant symptom exacerbation was defined a priori as a 20% or greater worsening in the PANSS total score along with a CGI-S score ≥3 after 8 weeks of therapy. Only patients who showed improvement in the PANSS total score of at least 20% from baseline at week 8 and who continued past week 8 were included in the analysis. Kaplan-Meier survival curves of time maintaining response were compared between treatment groups using the log-rank test.[37]

Post hoc analyses of efficacy outcomes including the BPRS total, PANSS total, SANS summary, and response rates were conducted excluding the three investigative sites that randomized less than at least one patient to each treatment arm.

All analyses were done on the intent-to-treat population, meaning all patients were included in the groups to which they were randomly assigned, even if a patient did not strictly adhere to the protocol. Statistical Analysis Software (SAS) was used to perform all statistical analyses.[38] For all analyses other than the primary efficacy analysis, main effects were tested at a two-sided α level of 0.05.

Results

Patient characteristics

A total of 339 patients (olanzapine N = 172, risperidone N = 167) were assigned to receive double-blind therapy. The treatment groups were comparable with respect to baseline demographic and illness characteristics

with one exception as noted below. The majority of the patients were men (64.9%), white (74.6%), and had a diagnosis of schizophrenia (81.7%), with 55.5% displaying a paranoid subtype. The courses of illness, according to DSM-IV, were mainly continuous (39.8%) or episodic with interepisode residual symptoms (34.5%). Among patients with courses of illness that were episodic with interepisode residual symptoms, continuous, or single episode in partial remission, 80.2% had prominent negative residual symptoms. The mean ± SD age of the patient population was 36.21 ± 10.73 years, with a mean ± SD age of onset of illness of 23.7 ± 8.0 years for the study cohort. The mean ± SD length of patients' current episodes was 153.8 ± 452.8 days. The majority of the patients (80.4%) had less than 10 previous episodes before entry into the study. Patients' baseline scores on the PANSS and its subscales, the BPRS, the SANS, and the CGI-S indicated that, overall, patients had severe and mixed symptomatology (positive, negative, and depressive). Patients also had a long history of illness. At baseline, 41.9% of the patients were inpatients. The only statistically significant between-treatment group difference in baseline measures was on the SANS summary score, which was significantly ($p = 0.044$) higher in the olanzapine treatment group (12.2) than in the risperidone treatment group (11.6).

Patient disposition

A total of 178 patients (52.5%) completed the study (olanzapine 57.6%; risperidone 47.3%, $p = 0.059$). Rates of discontinuation from the study were comparable for the olanzapine and risperidone treatment groups (satisfactory response, 0.0% vs. 1.2%; adverse event, 9.9% vs. 10.2%; lack of efficacy, 14.0% vs. 16.8%; lost to follow-up, 3.5% vs. 3.0%; patient decision, 10.5% vs. 14.4%, criteria not met/noncompliance, 4.7% vs. 5.4%, sponsor decision, 0.0% vs. 1.8%, respectively).

Medication use and compliance with study drug

The mean modal drug dose for the olanzapine treatment group was 17.2 ± 3.6 mg/day (starting dosage of 15 mg/day). The mean modal drug dose for the risperidone treatment group was 7.2 ± 2.7 mg/day (starting dosage of 1 mg twice daily). Over 50% of the patients treated with risperidone had a modal dose of 6 mg/day or less. Rates of compliance with medication instructions while participating in the study were similar (olanzapine 84.1%, risperidone 81.8%).

The mean daily anticholinergic medication use expressed in benztropine equivalents (milligrams of benztropine per day) was significantly lower ($p = 0.001$) in the olanzapine treatment group (0.27 mg ± 0.77) than in the risperidone treatment group (0.66 mg ± 1.27). A significantly smaller ($p = 0.006$) proportion of patients in the olanzapine treatment group (19.8%) than in the risperidone treatment group (32.9%) required at least one acute dose of an anticholinergic medication.

Efficacy

Change in efficacy measures. Both olanzapine-treated patients and risperidone-treated patients showed significant ($p < 0.001$) within-treatment group improvement from baseline to endpoint (LOCF) in PANSS total, PANSS positive, PANSS negative, PANSS general psychopathology, BPRS total, SANS summary, and CGI-S scores (Table 3). The olanzapine treatment group showed significantly greater improvement in the SANS summary score ($p = 0.020$). Additional analyses of the five SANS measures (affect, alogia, avolition, anhedonia, attention) showed that olanzapine was significantly superior in affect ($p = 0.011$), avolition ($p = 0.015$), and anhedonia ($p = 0.003$). The geographic region by therapy interactions were significant for the SANS summary score ($p = 0.043$).

The visitwise mean change (LOCF) in PANSS total is shown in Figure 1. The pattern of change was similar for the two treatment groups. The analyses of BPRS total, PANSS total, and SANS summary, without the three sites enrolling less than one patient to each treatment arm, did not alter the inferential outcomes.

Response rates. A significantly ($p = 0.049$) greater proportion of olanzapine-treated patients achieved a response of at least 40% improvement in PANSS total score than risperidone-treated patients (olanzapine 36.8% vs. risperidone 26.7%, $p = 0.049$) (Table 4). Moreover, nearly twice as many patients in the olanzapine treatment group as in the risperidone group achieved an improvement from baseline of at least 50% or more in PANSS total score. The analyses of response rates, without the three sites enrolling less than one patient to each treatment arm, did not alter the inferential outcomes.

Time maintaining response. Kaplan-Meier survival curves depicting time to a significant symptom exacerbation (≥20% worsening in PANSS total score and CGI-S ≥3) are shown in Figure 2. The two survival curves were significantly different ($p = 0.001$) and illustrate that patients in the olanzapine treatment group maintained their clinical response more often than patients in the risperidone treatment group. The estimated percentage of patients maintaining their acute response at 12 weeks and 28 weeks was 98.1% and 87.9% for the olanzapine treatment group versus 91.2% and 67.7% for the risperidone treatment group, respectively.

Safety

Treatment-emergent adverse events. The most commonly observed treatment-emergent adverse events (reported by at least 10% of the patients in either

TABLE 3. Mean change in efficacy measures, baseline to endpoint (LOCF)[a]

Measure	Therapy	N	Baseline Mean ± SD	Change Mean ± SD	*p* Value[b]
PANSS total score	Olz	166	96.3 ± 17.0	−28.1 ± 28.0	0.413[d,e]
	Risp	165	95.7 ± 16.2	−24.9 ± 23.2	
PANSS positive score	Olz	166	22.6 ± 5.5	−7.2 ± 8.1	0.654[c,d]
	Risp	165	22.5 ± 5.4	−6.9 ± 6.4	
PANSS negative score	Olz	166	26.0 ± 6.3	−7.3 ± 7.8	0.454[c]
	Risp	165	25.6 ± 5.4	−6.2 ± 6.6	
PANSS general psychopathology score	Olz	166	47.7 ± 9.4	−13.5 ± 14.4	0.311[c]
	Risp	165	47.6 ± 9.5	−11.8 ± 12.6	
PANSS depression item	Olz	166	3.0 ± 1.2	−1.1 ± 1.3	0.004[c]
	Risp	165	2.9 ± 1.3	−0.7 ± 1.4	
BPRS total score	Olz	166	36.7 ± 9.6	−17.0 ± 16.5	0.331[d,e]
	Risp	165	36.2 ± 9.0	−15.2 ± 13.3	
SANS summary score	Olz	157	12.2 ± 4.3[f]	−4.3 ± 5.3	0.020[d,e]
	Risp	151	11.6 ± 4.3[f]	−2.9 ± 3.8	
CGI-S score	Olz	166	4.6 ± 0.8	−1.1 ± 1.3	0.860[c,d]
	Risp	166	4.6 ± 0.8	−1.0 ± 1.1	

[a]N, number of patients with baseline and postbaseline measure; Olz, olanzapine 10, 15, or 20 mg/day; Risp, risperidone 4, 6, 8, 10, or 12 mg/day; PANSS, Positive and Negative Syndrome Scale; BPRS, Brief Psychiatric Rating Scale; SANS, Scale for the Assessment of Negative Symptoms; CGI-S, Clinical Global Impressions—Severity of Illness; LOCF, last-observation-carried-forward analysis.

[b]*p* Values are from the between-treatment group comparison; *p* values for mean change from baseline within treatment groups were all statistically significant ($p < 0.001$).

[c]*p* Values are from rank change.

[d]Significant treatment-by-geographic region interaction ($p < 0.100$).

[e]*p* Values are from least-squares mean change (raw data).

[f]Statistically significant difference at baseline ($p = 0.044$); *p* value is from between-group comparison.

treatment group) were somnolence, anxiety, weight gain, headache, insomnia, rhinitis, depression, and nausea. Overall, olanzapine-treated patients reported significantly fewer treatment-emergent adverse events than their risperidone counterparts. Through the 28 weeks of double-blind therapy (olanzapine, 23,622 patient-days of exposure; risperidone, 20,795 patient-days of exposure), one event (weight gain) was reported statistically significantly more often among the olanzapine-treated patients, whereas nine events (nausea, amblyopia, extrapyramidal syndrome, increased salivation, suicide attempt, abnormal ejaculation, back pain, creatine phosphokinase increases, and urinary tract infection) were reported statistically significantly more often among risperidone treated patients.

Consideration of gender-specific differences in adverse event profiles showed that no events were

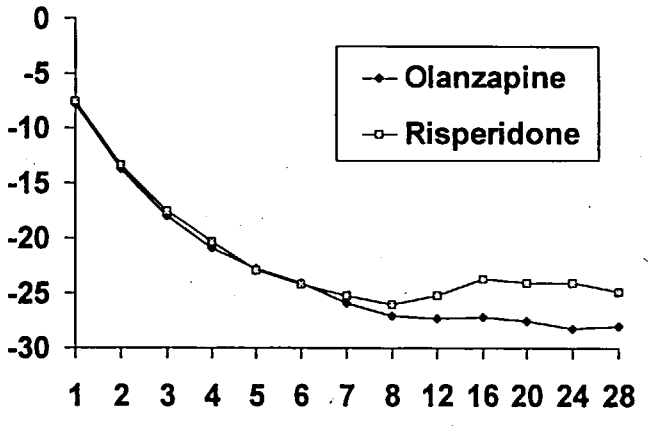

FIG. 1. Weekly observed-case analysis of change in PANSS total score for patients treated with olanzapine in a dose range of 10 to 20 mg/day or risperidone in a dose range of 4 to 12 mg/day. The numbers of patients active at weeks 0 (baseline), 1, 2, 3, 4, 5, 6, 7, 8, 12, 16, 20, 24, and 28, respectively, were as follows: olanzapine, N = 172, 166, 160, 150, 145, 142, 136, 132, 129, 124, 113, 112, 107, 102; risperidone, N = 167, 165, 154, 149, 146, 140, 139, 131, 125, 116, 100, 88, 83, 79.

TABLE 4. Response rates[a]

Criterion	Olanzapine (N = 166) n	Olanzapine (N = 166) %	Risperidone (N = 165) n	Risperidone (N = 165) %	*p* Value[b]
≥20% improvement[c]	102	61.5	104	63.0	0.766
≥30% improvement[c]	88	53.0	72	43.6	0.088
≥40% improvement[c]	61	36.8	44	26.7	0.049
≥50% improvement[c]	36	21.7	20	12.1	0.020

[a]N, number of patients with baseline and postbaseline measure; n, number of patients who met criterion.

[b]*p* Values are from Pearson's χ^2 test.

[c]Response rates based on percentage of improvement in Positive and Negative Syndrome Scale total score, last-observation-carried-forward analysis.

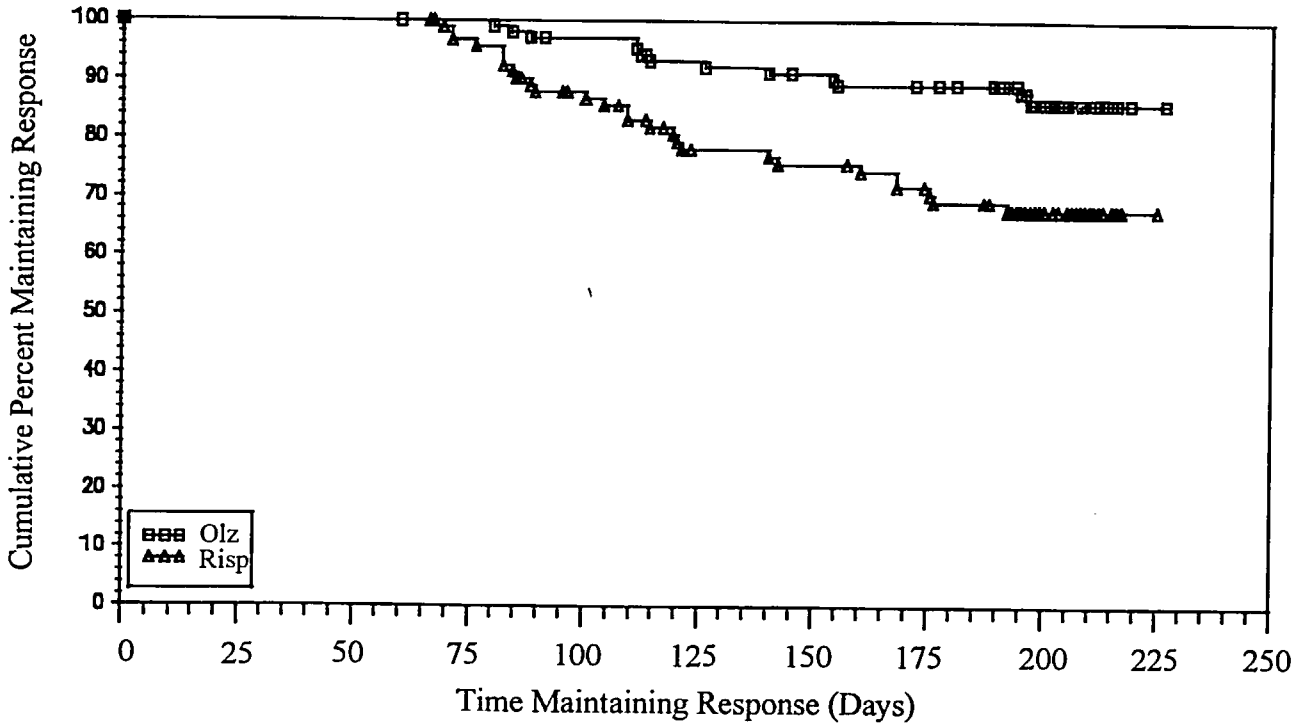

FIG. 2. Kaplan-Meier survival curves showing time maintaining response for patients in the olanzapine treatment group compared with patients in the risperidone treatment group. Time maintaining response is based on the PANSS and the CGI-S rating scales, week 28. The two survival curves are significantly different ($p = 0.001$). Olz, olanzapine in a dose range of 10 to 20 mg; Risp, risperidone in a dose range of 4 to 12 mg/day.

observed significantly more often in the male olanzapine-treated patients than in the male risperidone-treated patients. However, a statistically significantly ($p < 0.05$) greater proportion of the male risperidone-treated patients experienced treatment-emergent increased salivation, abnormal ejaculation, extrapyramidal syndrome, tachycardia, abnormal dreams, nausea, amblyopia, and abnormal thinking than their male olanzapine counterparts. Among female patients, a statistically significantly ($p < 0.05$) greater proportion of female olanzapine-treated patients experienced treatment-emergent weight gain and dry mouth, whereas a statistically significantly ($p < 0.05$) greater proportion of female risperidone-treated patients experienced treatment-emergent extrapyramidal syndromes, urinary tract infection, and suicide attempt.

Solicited treatment-emergent adverse events (AMDP-5). No solicited adverse event terms were statistically significantly more common among the olanzapine-treated patients than the risperidone-treated patients (Table 5). In contrast, a statistically significantly greater proportion of risperidone-treated than olanzapine-treated patients experienced treatment-emergent early waking, blurred vision, backache, breathing difficulties, delayed ejaculation, and increased dreams and

TABLE 5. Solicited adverse events with a statistically significant difference in incidence[a]

Group/Event Classification	Olanzapine (N = 167) n	Olanzapine (N = 167) %	Risperidone (N = 165) n	Risperidone (N = 165) %	*p* Value[b]
All patients					
Backache	11	6.6	22	13.3	0.040
Blurred vision	16	9.6	34	20.6	0.005
Breathing difficulties	12	7.2	24	14.5	0.031
Delayed ejaculation	3	1.8	12	7.3	0.016
Early waking	20	12.0	40	24.2	0.004
Increased dreams/ nightmares	19	11.4	32	19.4	0.043
Men only					
Akathisia	12	11.0	22	21.2	0.043
Delayed ejaculation	3	2.8	12	11.5	0.012
Hypersalivation	7	6.4	17	16.3	0.022
Increased dreams/ nightmares	8	7.3	22	21.2	0.004
Palpitations	6	5.5	15	14.4	0.029
Women only					
Backache	4	6.9	12	19.7	0.041
Blurred vision	6	10.3	15	24.6	0.042
Breathing difficulties	2	3.4	9	14.8	0.033
Early waking	5	8.6	18	29.5	0.004

[a]N, number of randomly assigned patients; n, number of patients reporting event.

[b]*p* Values are from Pearson's χ^2 test.

nightmares. A statistically significantly greater proportion of male risperidone-treated than male olanzapine-treated patients experienced treatment-emergent akathisia, increased dreams and nightmares, hypersalivation, palpitations, and delayed ejaculation. A statistically significantly greater proportion of female risperidone-treated patients than female olanzapine-treated patients experienced treatment-emergent early waking, breathing difficulties, backache, and blurred vision.

Treatment-emergent extrapyramidal adverse events (spontaneously reported). The proportions of patients with dystonic events and parkinsonian events were significantly lower in the olanzapine group when compared with the risperidone treatment group (1.7% vs. 6.0%, $p = 0.042$; 9.9% vs. 18.6%, $p = 0.022$). In addition, the proportion of patients with any extrapyramidal event was also significantly lower in the olanzapine treatment group than in the risperidone treatment group (18.6% vs. 31.1%, $p = 0.008$). The proportions of patients experiencing treatment-emergent akathisia events, dyskinetic events, and residual events were comparable between groups (9.9% vs. 10.8%, $p = 0.787$; 2.3% vs. 3.0%, $p = 0.702$; 1.7% vs. 0.6%, $p = 0.329$).

Treatment-emergent EPS as assessed by rating scales. Categorical analyses of the Simpson-Angus rating scale showed that significantly fewer olanzapine-treated than risperidone-treated patients experienced treatment-associated pseudoparkinsonism (12.5% vs. 22.3%, $p = 0.034$). Similarly, the proportion of patients in the olanzapine treatment group experiencing treatment-associated akathisia, based on the Barnes Akathisia Scale, was also significantly lower than that in the risperidone treatment group (15.9% vs. 27.3%, $p = 0.023$).

The proportions of patients with treatment-emergent dyskinetic symptoms at last visit, as assessed by categorical analysis of the AIMS according to the research diagnostic criteria of Schooler and Kane,[36] were significantly lower in the olanzapine treatment group than in the risperidone treatment group (4.6% vs. 10.7%, $p = 0.049$).

Weight, orthostatic blood pressure, and ECGs. Within both treatment groups, mean weight change from baseline to endpoint was statistically significant ($p < 0.001$). Between treatment groups, olanzapine-treated patients experienced significantly greater weight gain (4.1 ± 5.9 kg) than risperidone-treated patients (2.3 ± 4.8 kg, $p = 0.015$). Risperidone-treated patients demonstrated a significantly greater corrected QT (QT_c) interval prolongation than their olanzapine-treated counterparts (4.4 ± 35.1 milliseconds versus −4.9 ± 44.9 milliseconds, $p = 0.019$). There were no significant differences in change in orthostatic blood pressure (olanzapine, −1.63 ± 11.0 mm Hg; risperidone, 1.48 ± 13.3 mm Hg, $p = 0.088$).

Clinical laboratory evaluation. A significantly ($p < 0.001$) lower proportion of patients in the olanzapine treatment group experienced an elevation above standard reference ranges in prolactin concentration at any time during the study (51.2% vs. 94.4%). Moreover, fewer olanzapine-associated elevations were persistent. At endpoint, the proportion of risperidone-treated patients still elevated remained significantly ($p < 0.001$) higher than the proportion of olanzapine-treated patients still elevated (90.3% vs 36.0%). Because of abnormal baseline prolactin concentrations, 45% of olanzapine-treated patients and 55% of risperidone treated patients were excluded from the categorical prolactin analysis.

A significantly ($p = 0.019$) greater proportion of patients in the olanzapine group experienced elevated alanine transaminase/serum glutamic-pyruvic transaminase concentrations at any time than in the risperidone treatment group. No clinical sequelae were associated with these elevations in either medication group. The endpoint difference between the two treatment groups was not significant (olanzapine 1.8%, risperidone 0.6%, $p = 0.317$).

Similarly, a significantly greater proportion of patients in the olanzapine treatment group experienced treatment-emergent low neutrophil concentrations at any time (olanzapine 4.3%, risperidone 0.6%, $p = 0.034$), whereas the endpoint difference between the two treatment groups was not significant (olanzapine 1.8%, risperidone 0.6%, $p = 0.323$). None of the olanzapine-treated or risperidone-treated patients discontinued because of a decrease in neutrophil concentrations.

Quality of life

Mean change from baseline to endpoint on the Quality of Life Scale total score and on three of the subscales revealed no statistically significant between-treatment results (Table 6). However, the olanzapine treatment group demonstrated a significantly ($p = 0.011$) greater improvement in interpersonal relations. Furthermore, within-treatment-group mean improvements were statistically significant across all scores in both treatment groups.

Hospitalization

A history of hospitalization during the 6 months before study entry was evaluated and showed no significant difference in the prestudy rate of hospitalization between the two treatment groups (olanzapine 4.4 days/month; risperidone, 3.9 days/month). The overall hospitalization rate per patient during the study was 0.6 day/month greater for the risperidone treatment group than for the olanzapine treatment group (olanzapine 3.9 days/month; risperidone 4.5 days/month). This difference was

TABLE 6. Mean change in quality-of-life measures, baseline to endpoint (LOCF)[a]

Measure	Therapy	N	Baseline Mean ± SD	Change Mean ± SD	*p* Value: Within Group[b]	*p* Value: Between Group[c]
QLS total score	Olz	118	48.6 ± 21.5	13.4 ± 18.6	<0.001	0.074
	Risp	122	51.0 ± 23.2	8.8 ± 16.9	<0.001	
QLS common objectives and activities	Olz	118	5.8 ± 2.6	1.6 ± 2.4	<0.001	0.167
	Risp	122	6.0 ± 2.7	1.2 ± 2.2	<0.001	
QLS instrumental role	Olz	118	7.0 ± 6.1	1.7 ± 5.0	<0.001	0.388
	Risp	122	6.8 ± 6.2	1.1 ± 4.9	0.003	
QLS interpersonal relations	Olz	118	16.9 ± 9.3	5.4 ± 7.8	<0.001	0.011
	Risp	122	18.5 ± 9.4	2.8 ± 6.6	<0.001	
QLS intrapsychic foundation	Olz	118	18.9 ± 7.7	4.8 ± 7.5	<0.001	0.374
	Risp	122	19.5 ± 8.5	3.7 ± 6.7	<0.001	

[a]N, number of patients with baseline and postbaseline measure; Olz, olanzapine in a dose range of 10 to 20 mg/day; Risp, risperidone in a dose range of 4 to 12 mg/day; QLS, Quality of Life Scale; LOCF, last-observation-carried-forward analysis.
[b]*p* Values are from Wilcoxon signed-rank test.
[c]*p* Values are from least-squares mean change (raw data).

attributed to a higher rate of psychiatric hospitalization among the risperidone patient group.

Discussion

This is the first large-scale, prospective, double-blind evaluation of two novel antipsychotic agents. The primary objectives were to evaluate the relative safety and efficacy of the two drugs in the treatment of patients with schizophrenia, schizophreniform disorder, and schizoaffective disorder during 28 weeks. In addition, the study was designed to test a number of secondary hypotheses to assess the comparative "atypicality" of these two therapies.

Results of this first study showed that both olanzapine (10 to 20 mg/day) and risperidone (4 to 12 mg/day) were effective in reducing the severity of overall psychotic symptoms. However, olanzapine exhibited statistically significantly greater efficacy in improving SANS-rated negative symptoms ($p = 0.020$) and response rates, and a greater proportion of olanzapine-treated than risperidone-treated patients experienced ≥40% improvement in their PANSS total score ($p = 0.049$). Further inspection of the scope of symptom improvement revealed that nearly twice as many olanzapine-treated (21.7%) as risperidone-treated patients (12.1%) achieved a 50% or greater improvement in PANSS total from baseline ($p = 0.020$). The results on the SANS and the PANSS negative score differed in the present study, perhaps because the SANS was designed specifically to assess negative symptoms and samples a wider spectrum of negative symptoms than the PANSS. Additionally, it may be noted that a factor contributing to the difference was the olanzapine-treated group had a higher baseline score on the SANS, and the observed difference may represent greater random regression on the part of the olanzapine-treated group. Finally, the difference in the SANS must be considered in light of the significant treatment-by-geographic region interaction.

The findings of differential treatment effects on negative symptoms in schizophrenia are of interest. Negative[39] symptom comorbidity in schizophrenia has been associated with impaired functional well-being, greater disability, and mortality. Both olanzapine and risperidone have previously been shown to improve negative symptoms.[9–15] Moreover, in a recent paper by Tollefson and Sanger[15] a path analysis demonstrated that olanzapine exhibited significantly greater direct improvement on SANS scores than either placebo or haloperidol. Similar results have been demonstrated with risperidone and clozapine.[40, 41] The relative primary negative symptom effects of these agents might be best tested in a cohort with predominant deficit state features.

Schizophrenia is a chronic disease with a high mortality rate. About 10% of schizophrenic patients commit suicide.[42] In one study, up to 40% of schizophrenic patients reported suicidal ideation, with 23% reporting attempted suicide.[43] The economic burden of schizophrenic patients who commit suicide has been estimated to be around $7 billion in the United-States.[44] In the present study, the rate of suicide attempts based on assessment of treatment-emergent adverse events was statistically significantly lower with olanzapine (0.6%; one patient with one attempt) than risperidone (4.2%, $p = 0.029$; seven patients, each with one attempt). This potentially important difference merits validation in future studies.

One goal of psychopharmacologic research for newer antipsychotics is to replicate the ability of clozapine to separate antipsychotic efficacy from troublesome extrapyramidal side effects. Extrapyramidal side

effects are thought to limit the efficacy of conventional neuroleptics, contribute to poor compliance leading to relapse, and amplify patients' poor quality of life.[45] In this study, olanzapine treatment resulted in significantly fewer extrapyramidal side effects than treatment with risperidone on both self-reported treatment-emergent adverse events and categorical change on objective rating instruments. The higher incidence of EPS with risperidone was evident despite statistically significantly more frequent use of anticholinergic drugs among risperidone-treated patients and gradual titration of risperidone, starting at a dosage of 1 mg two times daily. The higher rate of EPS reported in this study is also consistent with reports in the literature indicating that risperidone is associated with dose-dependent treatment-emergent EPS.[11, 12, 46]

From a pharmacodynamic perspective, both agents are potent 5-HT_2 blockers. However, risperidone lacks affinity for muscarinic receptors, which have been reported to modulate dopamine and mitigate against EPS.[6] Alternatively, it may not be surprising to find that there is a difference in treatment-emergent dyskinesia between the two treatment groups because researchers have found that acute EPS may predict increased risk for tardive dyskinesia.[47] However, the diagnosis of treatment-emergent tardive dyskinesia cannot be established definitively from these results because such results are subject to multiple confounds including nonstandardized documentation of tardive dyskinesia at baseline, varying lengths of treatment, the absence of a criterion for persistence of dyskinetic symptoms, and the possibility that some events represented drug-withdrawal dyskinesia. However, this finding should call for a more thorough evaluation of tardive dyskinesia potential between novel antipsychotics such as olanzapine and risperidone.

No statistically significant differences were detected between olanzapine and risperidone in spontaneously reported akathisia, dyskinetic, and residual events. Although spontaneously reported adverse events are of importance in assessing drug side effects, this method may be considered less reliable than well-standardized rating instruments in assessing EPS such as akathisia and dyskinesia. For example, akathisia could be mistaken for agitation, a manic reaction, or depression.[48]

Despite the *in vitro* muscarinic differences of the two drugs, it is of interest to note that patients treated with risperidone reported more apparent anticholinergic adverse events including blurred vision, amblyopia, and palpitation than patients treated with olanzapine. Although the *in vitro* preclinical pharmacology of olanzapine might predict anticholinergic potential, the present study results agree with those of previous clinical trials[9, 10, 14] in demonstrating that the *in vivo* anticholinergic profile of olanzapine is minimal. One possible explanation for the higher incidence of such events among risperidone-treated subjects may relate to their greater use of antiparkinsonian drugs to control treatment-emergent EPS. However, risperidone-treated patients who did not use benztropine also reported a higher frequency of amblyopia (4.1% vs. 1.2%, $p = 0.106$) and palpitation (1.6% vs. 0.0%, $p = 0.093$) than the entire olanzapine-treated cohort.

It is well established that antipsychotic drugs that block dopamine neurotransmission may cause a sustained increase in prolactin secretion, presumably mediated via dopaminergic tuberoinfundibular pathways.[49] The possible consequences of chronic prolactin elevation include gynecomastia, galactorrhea, amenorrhea, sexual dysfunction, and predisposition to osteoporosis. The relative absence of a sustained effect on prolactin concentrations represents a potential criterion for "atypicality," that is, evidence for a selective and/or nondopamine dominant pharmacology. Results in this study demonstrated such a profile among subjects treated with olanzapine who experienced significantly lower incidence of prolactin elevation. Similar results have been reported for olanzapine compared with haloperidol.[9, 14] Olanzapine has also been shown to be associated with prolactin elevation comparable to that with placebo after 6 weeks.[9, 10]

Sexual dysfunction in schizophrenic patients has not been extensively studied in the literature. Aizenberg and colleagues[50] reported that most neuroleptic agents influence patients' sexual function and may result in noncompliance. The present study showed that olanzapine treatment was associated with statistically significantly less sexual dysfunction, as assessed by incidence of treatment-emergent and solicited adverse events, than treatment with risperidone. Sexual dysfunction has been reported previously with risperidone.[12] This may be related to its effect on prolactin. Sexual dysfunction has previously been reported in conjunction with elevated plasma prolactin concentrations among male patients treated with neuroleptics.[51] Another possible explanation is the differential blocking effect of the α-adrenergic receptors.[52]

Two features of this clinical trial design merit discussion. First is the selection of the risperidone dose range. The choice of a dose range, instead of a fixed dose, provided investigators flexibility to optimize the naturalistic dose best suited for each patient. The dose range of risperidone in the study presented here was dictated by the package labeling that was approved by the U.S. Food and Drug Administration, which is current as of the time of submission of this article. Current clinical practice with risperidone may involve slower dose titration and efforts to use dosages in the 4 mg/day to 6

mg/day range. If a slower dose titration had been used for risperidone in this protocol, it might be speculated that there would have been a reduced incidence of EPS. However, a categorical analysis of the Barnes Akathisia and Simpson-Angus scales on a by-visit basis failed to demonstrate that the overall differences in the incidences of parkinsonism and akathisia were due to differences during the initial weeks of study participation.

In a review of the clinical experience with risperidone, Marder[53] reported that more than 50% of risperidone-responding patients had received dosages above 6 mg/day. Furthermore, across a dose range of 1 to 12 mg, risperidone was associated with a lower incidence of EPS than 10 mg of haloperidol. In another review by Simpson and Lindenmayer,[46] even in patients treated at 16 mg/day of risperidone, the mean change scores in the Extrapyramidal Symptom Rating Scale (ESRS) were lower than in the haloperidol group. The mean modal dose of olanzapine was 17.2 ± 3.6 mg/day (28 weeks). The starting olanzapine dosage of 15 mg/day (approved range, 10 to 20 mg/day) was chosen to evaluate the EPS/prolactin profile of olanzapine at a maximal dose and one exceeding the currently recommended starting dosage of 10 mg/day.[10] This higher starting dose may have biased against olanzapine with regard to observation of adverse events. In light of the low incidence of side effects associated with 15 mg/day of olanzapine, it is not surprising that the investigators rarely decreased the dose below this value.

The second discussion point relates to the exclusion criteria used to select the study population presented in this study. This study, initiated before regulatory approval to market olanzapine, necessarily excluded certain special patient populations, for example, those with serious concomitant medical illnesses. In a broader and more naturalistic clinical practice condition, the patients would potentially be more heterogeneous, and the results presented in this study, although likely applicable, will need confirmation.

In conclusion, both olanzapine in a dose range of 10 to 20 mg/day and risperidone in a dose range of 4 to 12 mg/day were safe and effective in reducing overall psychopathology in a patient population with chronic schizophrenia and related psychotic disorders. However, olanzapine demonstrated several selective advantages, including a statistically significantly superior improvement of negative symptoms, a higher rate of response, and a significantly greater proportion of patients maintaining an initial response. In addition to these efficacy advantages, the overall incidence of extrapyramidal side effects, hyperprolactinemia, and sexual dysfunction was statistically significantly lower with olanzapine. The relevance of higher incidences of weight gain (olanzapine) and QT_c prolongation (risperidone) remains to be determined. Overall, the study presented here suggests that olanzapine closely resembles the profile of an "atypical" antipsychotic agent. Additional studies across more heterogeneous populations that use various dosing strategies will be of interest to confirm the differential clinical effectiveness of olanzapine observed in this trial.

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