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Olanzapine vs risperidone in the management of schizophrenia: a randomized double-blind trial in Australia and New Zealand

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Abstract

Improved drug therapy for schizophrenia may represent the best strategy for reducing the costs of schizophrenia and the recurrent chronic course of the disease. Olanzapine and risperidone are atypical antipsychotic agents developed to meet this need. We report a multicenter, double-blind, parallel, 30-week study designed to compare the efficacy, safety, and associated resource use for olanzapine and risperidone in Australia and New Zealand. The study sample consisted of 65 patients who met DSM-IV criteria for schizophrenia, schizoaffective disorder, or schizophreniform disorder. Olanzapine-treated patients showed a significantly greater reduction in Positive and Negative Syndrome Scale (PANSS) total, Brief Psychiatric Rating Scale (BPRS) total, and PANSS General Psychopathology scores at endpoint compared to the risperidone-treated patients. Response rates through 30 weeks showed a significantly greater proportion of olanzapine-treated patients had achieved a 20% or greater improvement in their PANSS total score compared to risperidone-treated patients. Olanzapine and risperidone were equivalent in their improvement of PANSS positive and negative scores and Clinical Global Impression-Severity of Illness scale (CGI-S) at endpoint. Using generic and disease-specific measures of quality of life, olanzapine-treated patients showed significant within-group improvement in most measures, and significant differences were observed in favor of olanzapine over risperidone in Quality of Life Scale (QLS) Intrapsychic Foundation and Medical Outcomes Study Short

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Form 36-item instrument (SF-36) Role Functioning Limitations—Emotional subscale scores. Despite the relatively small sample size, our study suggests that olanzapine has a superior risk:benefit profile compared to risperidone.

Keywords: Olanzapine; Risperidone; Schizophrenia; Quality of life

1. Introduction

Schizophrenia is a disease of low prevalence, but characterized by a chronic recurrent course (Kane, 1996; Jablensky et al., 1999). As many as 30–40% of patients may exhibit an inadequate or poor response to conventional (typical) antipsychotic agents (Meltzer, 1992; Kane, 1992; Lieberman, 1993). A substantial proportion of schizophrenic patients may also be noncompliant with their medication, leading to a "revolving door" of relapse and readmission, with subsequent progressive social and functional deficits. Estimates of noncompliance have ranged between 11% and 80% (Corrigan et al., 1990). A common reason for noncompliance is the occurrence of side effects, particularly those of extrapyramidal origin (Meltzer, 1992; Van Putten, 1974). It is estimated that up to 50% of patients will experience serious side effects on conventional medication (Kane and Lieberman, 1992). In addition, a recent community-based survey of patients with psychosis in Australia found that 84% of participants reported one or more side effects due to their medication, and of these side effects, extrapyramidal sides effects were the most prominent (Jablensky et al., 1999). The focus of new drug development for treatment of schizophrenia has, therefore, been to synthesize compounds capable of alleviating symptoms, particularly negative symptoms, which is commonly unresponsive to classical antipsychotics, and to synthesize compounds less likely to produce extrapyramidal side effects (Moore et al., 1993). These newer (atypical) antipsychotics have been the subject of numerous randomized controlled trials comparing them with the older conventional agents. However, there is a lack of well-designed studies making head-to-head comparisons. Such studies are necessary to assist in the evaluation of the newer agents.

The quality of life of schizophrenic individuals will relate to the symptomatic relief of antipsychotic treatment in addition to the freedom from treatment-emergent side effects. These factors are also likely to promote a return to active economic participation and, therefore, to have an impact on the cost effectiveness of treatment. Studies of newer antipsychotics should include a wider range of outcome measures beyond the usual safety and efficacy (such as quality of life, functioning, and economic measures).

Olanzapine is a thienobenzodiazepine with a high affinity for serotonin 5-HT_2, histamine H_1, α_1-adrenergic, D_1, and D_2 dopamine receptors (Moore et al., 1992, 1993). In well-controlled blinded clinical trials, it has been shown to have a better efficacy and side-effect profile than the traditional antipsychotic haloperidol (dose range; 5 to 20 mg/day) and is more efficacious in the treatment of negative symptoms (Beasley et al., 1996; Tollefson et al., 1997). At a standard dose of 5 to 15 mg/day, olanzapine also shows superior efficacy to placebo and ineffective dose olanzapine in the maintenance therapy of schizophrenia (Dellva et al., 1997). Risperidone is a benzisoxazole derivative. Its greatest affinity is for serotonin 5-HT_2, histamine H_1, α_1-adrenergic, and dopamine D_2 sites (Moore et al., 1993). It has been shown to be superior to typical antipsychotics in numerous clinical studies (Ceskova and Svestka, 1993; Heinrich et al., 1994; Marder and Meibach, 1994). While risperidone has been in clinical use in Australia and New Zealand for several years, olanzapine has only recently been approved for use in these countries. Even though the clinical profile of the two drugs puts both in the league of new antipsychotics described as "atypical" (Casey, 1992), the two differ in some important ways: structure, profile of receptor binding affinities, animal neuropharmacology, and pharmacokinetics (Moore et al., 1993; Tran et al., 1997). It is hypothesized that, in view of such differences, both compounds will show not only differential clinical profile in regard to efficacy and treatment-emergent side effects, but also in terms of illness-related quality of life and health care resource utilization. An earlier multicenter, double-blind comparison

of the two drugs found that olanzapine demonstrated significantly greater efficacy in negative symptoms, produced greater overall response rate, and was temporally associated with fewer extrapyramidal adverse events (Tran et al., 1997). This paper presents the results of a similar study conducted in Australia and New Zealand to further address the question of the relative superiority of either of the two drugs in the treatment of psychotic disorders.

2. Methods

2.1. Study design

The study was conducted at six sites across Australia and two sites in New Zealand. Each site's institutional ethical review board approved the study protocol, and signed informed consent was obtained from all eligible patients. The study design included a washout period of 2 to 9 days, a 30-week double-blind therapy phase in which patients were randomized to receive olanzapine 10 to 20 mg/day or risperidone 4 to 8 mg/day, and an optional 48-week extension phase. The protocol included follow-up of patients after stopping study medication for assessment of quality of life and resource utilization. Data are presented here for the 30-week therapy phase. Because of patient dropout from both arms and the difficulty in following up patients who stopped study medication, the study was terminated after the 30-week therapy phase.

Patients randomized to receive olanzapine began therapy with 15 mg/day, administered once per day. From the second week on, investigators were able to adjust the daily dose upward or downward in the allowed range of 10 to 20 mg/day. Patients randomized to receive risperidone titrated their dose from 1 mg twice daily on Day 1 to 2 mg twice daily on Day 2 and then 3 mg twice daily on Days 3 through 7. From the second week on, investigators were able to adjust the daily dose upward or downward in the allowed range of 4 to 8 mg/day with blinding maintained by use of a double dummy design.

2.2. Randomization and blinding

Patients were assigned to a treatment group by random allocation using a computer-generated random number list. The study randomization list was not accessible to study sites. Once randomized, envelopes with the randomization code were available to the study sites, but were opened only if medically essential, and the patient was withdrawn from the study. Study envelopes were returned from sites on completion of the study. Blinding of study medication was ensured in spite of the difference in dosing schedules by use of a double dummy design.

2.3. Subjects

Patients were aged 18 years or over, met DSM-IV criteria for schizophrenia or schizophreniform disorder of at least moderate severity, and had scores of greater than 36 (on items scored 1 to 7) on the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1962) extracted from the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987). Patients could begin the study as either inpatients or outpatients. Pregnant female patients were excluded, as were patients who had failed to show a response to clozapine at a dose of >400 mg/day for at least 6 weeks.

2.4. Assessment

Clinical assessment was carried out at a screening visit, followed by baseline assessment after the washout period. Patients were assessed weekly from baseline until Visit 8 and then at 4-week intervals through to Visit 14 (30 weeks). A standard medical history, physical examination, electrocardiogram, and laboratory profile were obtained at the screening visit. Physical examination and ECG were repeated after 6 weeks of therapy or at early discontinuation.

Efficacy assessment included the PANSS total and its subscales (positive, negative, and general psychopathology), the BPRS total extracted from the PANSS, and the Clinical Global Impression-Severity of Illness scale (CGI-S) (Guy, 1976). Videotapes of patient interviews were used to train staff at study initiation, and a computerized program assessed interrater reliability (Lambert, 1998).

Adverse events were detected by clinical evaluation and spontaneous report at each visit, and captured as treatment-emergent adverse events using the screening period as baseline. Extrapyramidal symp-

toms (EPS) and akathisia were further assessed with the Simpson–Angus Scale (Simpson and Angus, 1996) and the Barnes Akathisia Scale (Barnes, 1989). Patients' quality of life was assessed with the Quality of Life Scale (QLS) (Heinrichs et al., 1984) and with the Medical Outcomes Study Short Form 36-item instrument (SF-36) (Stewart et al., 1988). Medical resource utilization and various functional and economic indicators were collected using a case report form specifically designed for this study.

2.5. Statistical methods

The primary objectives of this study were to assess efficacy and safety in patients receiving olanzapine vs. those receiving risperidone. Effect on resource utilization, quality of life, and functional measures was also evaluated. All analyses were done on an intent-to-treat basis, meaning all patients were included in the treatment groups to which they were randomized, even if the patient did not strictly adhere to the protocol. When last-observation-carried-forward (LOCF) change from baseline to endpoint was assessed, patients were included in the analysis only if they had a baseline and a postbaseline measure. The baseline measure was the Visit 2 observation. An endpoint measure was the last measure observed during the 30 weeks of double-blind therapy.

Baseline patient characteristics were summarized for each treatment group and also combined across treatment groups. All randomized patients were included. Frequencies were analyzed using Pearson's χ^2-test and means were analyzed using analysis of variance (ANOVA) with only the treatment term used in the model. Concomitant medications and reasons for discontinuation were compared between treatment groups by a Pearson's χ^2-test. Proportions of patients taking at least one dose of an anticholinergic drug were compared between treatment groups using Pearson's χ^2-test.

The analysis of change from baseline to endpoint (LOCF) in PANSS total was the primary efficacy analysis, with change assessed using an ANCOVA model with terms for treatment, geographic region, treatment-by-geographic region interaction, and baseline measurement included. Similar analyses were done on BPRS total, PANSS subscales, and CGI-Severity as secondary analyses. Response rates (LOCF) were calculated for those patients who achieved reductions in PANSS total scores of 20%, 30%, 40%, and 50% from baseline to endpoint. Treatment groups were compared using Pearson's χ^2-test.

The incidence of treatment-emergent adverse events was assessed by Pearson's χ^2-test overall and by gender. Treatment effect on change from baseline to endpoint in weight and vital signs was assessed using an ANOVA model with terms for treatment, geographic region, and treatment-by-geographic region interaction. Proportions of patients whose ECG's changed from normal at baseline to abnormal at endpoint were compared using Pearson's χ^2-test. Proportions of patients with treatment-emergent abnormal, high, or low laboratory values based on reference ranges were compared at endpoint and any time after baseline. Patients with abnormal values at baseline were not included in these analyses. Treatment groups were compared using Pearson's χ^2-test.

Pseudoparkinsonism or akathisia were analyzed by determining the proportion of patients with a score of more than 3 (Simpson–Angus scale) at any postbaseline visit among those with a score of 3 or less at baseline, or a score of ≥ 2 (Barnes scale) among those with a score of less than 2 at baseline, respectively. Treatment groups were compared using Pearson's χ^2-test.

All analyses were done using Statistical Analysis Software (SAS) (Anon., 1990; *SAS/STAT User's Guide*). For all analyses, main effects were tested at a two-sided α level of 0.05.

3. Results

3.1. Patient characteristics

A total of 65 patients were randomized into this study (olanzapine $N=32$, risperidone $N=33$). However, three patients randomized to the risperidone group dropped out between randomization and the next visit. Therefore, they were included in the safety analysis, but not the efficacy analysis as per the protocol plan. The two groups were comparable in almost all baseline demographics and severity of illness (Table 1). The DSM-IV courses of illness were mainly continuous (34% of olanzapine patients and 23% of the risperidone patients) and episodic with

Table 1
Patient baseline characteristics

Treatment (randomised patients)	Olanzapine ($N=32$)	Risperidone ($N=33$)	p-Value
Mean age ± S.D. (years)	35.6 ± 11.4	34.8 ± 9.4	0.764 *
Gender—no. (%)			0.515 **
Male	20 (62.5)	18 (54.5)	
Female	12 (37.5)	15 (45.5)	
Ethnicity—no. (%)			0.140 **
Caucasian	31 (96.9)	27 (81.8)	
East/S.E. Asian	0	1 (3.0)	
Other ethnic	1 (3.1)	5 (15.2)	
Efficacy measures available	$N=32$	$N=30$	
PANSS total score	94.7 ± 18.4	88.9 ± 15.7	
BPRS total score	35.0 ± 10.5	32.1 ± 8.6	
Duration of hospitalization in 12 months prior	18.75 days	11.47 days	

* Means are analysed using a type-III sums-of-squares analysis of variance.
** Frequencies are analysed using a χ^2-test.

interepisode residual symptoms (34% of olanzapine patients and 40% of the risperidone patients). Baseline scores on the PANSS and its subscales, the BPRS total, and CGI-Severity scores indicated that both groups had a moderate severity of illness. On all these measures the olanzapine group scored slightly higher at baseline, but the differences were not significant. Hospitalization rates during the 12 months prior to randomization were similar between the two groups ($n=22$ and $n=20$ for the olanzapine- and risperidone-treated groups, respectively); however, the average duration of stay was higher for the olanzapine group (18.75 days/patient) than for the risperidone group (11.47 days/patient).

3.2. Patient disposition

A total of 29 patients completed the study to the 30-week endpoint. Rates of discontinuation from the study were comparable between groups (Table 2).

3.3. Medication use and compliance with study drug

The mean modal dose for the olanzapine treatment group was 17.2 ± 2.8 mg/day (starting dose: 15 mg/day). The mean modal dose for the risperidone group was 6.6 ± 1.6 mg/day (starting dose of 2 mg/day titrated to 6 mg/day by Day 3). More olanzapine patients (81.3%) had exposure to study drug of more than 91 days compared to risperidone patients (71.9%).

A smaller, nonsignificant ($p=0.137$) number of patients in the olanzapine group (12.5%) required at least one dose of anticholinergic medication compared with the risperidone group (27.3%).

3.4. Efficacy

3.4.1. Change in efficacy measures

The olanzapine treatment group showed significantly greater improvement than the risperidone treatment group in PANSS total ($p=0.038$), PANSS general psychopathology ($p=0.016$), and BPRS total scores ($p=0.012$) (Table 3). There were no significant between group differences in the improvements in PANSS positive or negative or CGI-Severity scores.

Both the olanzapine and risperidone treatment groups showed significant ($p<0.001$) within-group

Table 2
Patient disposition—week 30

Reason for Discontinuation	Olanzapine ($N=32$)		Risperidone ($N=33$)		Total ($N=65$)	
	n	%	n	%	n	%
Lack of efficacy	6	18.8	11	33.3	17	26.2
Patient decision	4	12.5	5	15.2	9	13.8
Criteria not met/ compliance	3	9.4	1	3.0	4	6.2
Sponsor decision	0	0	1	3.0	1	1.5
Physician decision	2	6.3	3	9.1	5	7.7
Completed	17	53.1	12	36.4	29	44.6

N = number of randomized patients, n = frequency. No statistically significant differences.

Table 3
Efficacy measures—mean change from baseline to week 30 (LOCF)

Measure	Therapy	Baseline		Endpoint		N	Change		p-Value	
		mean	S.D.	mean	S.D.		mean	S.D.	Within Group	vs. Ris
PANSS total score	Olz	94.7	18.4	66.5	14.6	32	− 28.2	20.8	< 0.001	0.038
	Ris	88.9	15.7	72.6	22.5	30	− 16.3	16.3	< 0.001	
PANSS positive score	Olz	22.2	5.7	16.0	4.4	32	− 6.2	5.8	< 0.001	0.371
	Ris	20.6	5.9	16.5	6.7	30	− 4.1	5.4	< 0.001	
PANSS negative score	Olz	24.6	6.6	18.3	6.0	32	− 6.3	6.6	< 0.001	0.122
	Ris	24.0	5.8	19.9	6.0	30	− 4.1	5.3	< 0.001	
PANSS gen. psych. score	Olz	47.9	9.9	32.2	7.1	32	− 15.8	10.5	< 0.001	0.016
	Ris	44.3	7.3	36.2	12.2	30	− 8.1	9.1	< 0.001	
BPRS total score	Olz	35.0	10.5	18.6	7.1	32	− 16.4	12.3	< 0.001	0.012
	Ris	32.1	8.6	23.3	12.2	30	− 8.8	9.2	< 0.001	
CGI severity score	Olz	4.7	0.7	3.6	0.8	32	− 1.1	0.8	< 0.001	0.076
	Ris	4.3	1.0	3.8	1.2	30	− 0.5	1.1	0.028	

N = number of patients with a baseline and at least one postbaseline measure. Olz = olanzapine 10 to 20 mg/day; Ris = risperidone 4 to 8 mg/day; PANSS = Positive and Negative Syndrome Scale; BPRS = Brief Psychiatric Rating Scale; CGI Severity = Clinical Global Impressions—Severity of Illness; LOCF = last observation carried forward analysis; gen. psych = general psychopathology.
Mean baseline measurement is for all randomized patients with at least one postbaseline measure.

improvement from baseline to endpoint (LOCF) in PANSS total, PANSS positive, PANSS negative, PANSS general psychopathology, and BPRS total scores (Table 3). The within-group improvement for CGI-Severity scores were significant in the olanzapine treatment group at $p < 0.001$ and were significant for the risperidone treatment group at $p = 0.028$.

Analysis of change in PANSS total by visit showed similar change in both groups over the 30-week period.

3.4.2. Response rates

After 30 weeks, more olanzapine-treated patients achieved a response of at least 20% improvement in PANSS total score than risperidone-treated patients ($p = 0.01$) (Table 4). The percentage of olanzapine-treated patients who achieved a response of at least 30%, 40%, and 50% improvement in PANSS total score was greater in all groups than risperidone-treated patients.

3.5. Safety

3.5.1. Treatment-emergent adverse events

The most commonly observed adverse events (reported by at least 10% of patients in either treatment group) are shown in Table 5. Over the study period of 30 weeks, there were no events that occurred statistically significantly more frequently in olanzapine-treated patients than in risperidone-treated patients (Table 5). Significantly more risperidone-treated patients reported somnolence, constipation, and rhinitis ($p \leq 0.05$).

3.5.2. Treatment-emergent extrapyramidal adverse events

There were no significant differences between the olanzapine group and the risperidone group in the spontaneously reported incidences of akathisia, dyskinesia, cogwheel rigidity, or other extrapyramidal symptoms. In addition, when assessed by rating scales, no significant differences between risperidone-treated patients and olanzapine-treated patients

Table 4
PANSS total score response rates—week 30

	Olanzapine (N = 32)		Risperidone (N = 30)	
	n	%	*n*	%
≥ 20% Improvement	24	75.0	14	46.7 *
≥ 30% Improvement	15	46.9	10	33.3
≥ 40% Improvement	7	21.9	4	13.3
≥ 50% Improvement	3	9.4	2	6.7

PANSS = Positive and Negative Syndrome Scale, *N* = number of patients with baseline and postbaseline measure, *n* = frequency.
* $p = 0.01$, Olanzapine vs. risperidone, (χ^2).

Table 5
Most commonly reported treatment-emergent adverse events (more than 10% of patients in either treatment group)

Event classification	Olanzapine ($N=32$)		Risperidone ($N=33$)	
	n	%	*n*	%
Somnolence	9	28.1	20	60.6 *
Headache	7	21.9	9	27.3
Vomiting	7	21.9	4	12.1
Abdominal pain	6	18.8	3	9.1
Akathisia	6	18.8	5	15.2
Dysmenorrhoea[a]	2	16.7	0	0
Accidental injury	5	15.6	1	3.0
Myalgia	5	15.6	1	3.0
Weight gain	5	15.6	2	6.1
Depression	4	12.5	6	18.2
Increased appetite	4	12.5	2	6.1
Anxiety	3	9.4	4	12.1
Asthenia	3	9.4	6	18.2
Dizziness	3	9.4	4	12.1
Increased salivation	2	6.3	5	15.2
Insomnia	2	6.3	7	21.2
Impotence[b]	1	5.0	2	11.1
Constipation	1	3.1	6	18.2 *
Rhinitis	1	3.1	7	21.2 *

N = number of patients randomized, n = number of patients reporting event.
[a] Denominator used was for females only ($N=27$).
[b] Denominator used was for males only ($N=38$).
* $p \leq 0.05$, Olanzapine vs risperidone (χ^2).

demonstrating treatment-emergent EPS as assessed by the Barnes Akathisia Scale or by the Simpson–Angus Scale were observed.

3.5.3. Weight, ECGs, and orthostasis

Both treatment groups showed significant ($p<0.001$) increases in weight from baseline to endpoint. The mean gain was 4.9 kg for the olanzapine group and 4.5 kg for the risperidone group. Although investigators reported a small number of olanzapine-treated patients gained a significant amount of weight, the gains were not significantly different ($p=0.673$) between the two groups. No significant differences were seen in the occurrence of abnormal ECGs among patients with normal ECGs at baseline or in the change from baseline in orthostasis.

3.5.4. Clinical laboratory values

Changes in blood chemistry values were relative to reference ranges during therapy for patients with values within the normal range at baseline. In addition, significantly more olanzapine-treated patients compared to risperidone-treated patients showed a reduction in total protein and non-fasting glucose levels ($p=0.039$ and 0.042, respectively). No clinical sequelae were associated with any of these changes. At study endpoint, there were no statistically significant differences for any of the laboratory analytes measured.

3.6. Quality of life

The olanzapine-treated group showed statistically significant changes from baseline to endpoint in total score and three of the four subscales of the Quality of Life Scale, as shown in Table 6. Only the Instrumental Role subscale did not show significant improvement from baseline. The risperidone-treated group failed to show statistically significant improvement from baseline to endpoint on total score or on any subscale score. Between the two treatment groups, olanzapine-treated patients had a significant improvement in the QLS Intrapsychic Foundation subscale score over risperidone-treated patients ($p=0.013$).

Quality-of-life assessment using the SF-36 shows within-group changes from baseline to endpoint were statistically significant for the olanzapine-treated group on all subscales except Role Functioning Limitations due to Physical Health ($p=0.058$) and Self-Reported Change ($p=0.133$). Within-group changes for the risperidone-treated group were statistically significant for Bodily Pain subscale only ($p=0.041$) (Table 7).

Between-treatment comparisons showed the olanzapine-treated patients reported statistically significantly greater changes compared to the risperidone-treated patients in Role Functioning Limitations due to Emotional Health ($p=0.046$).

3.7. Hospitalization and other health care resource use

Both groups experienced a similar number of episodes of hospitalization in the 12 months prior to randomization (data not shown). At the 30-week endpoint, the cumulative number of episodes of hospitalization was greater for olanzapine-treated patients than for risperidone-treated patients. When the num-

Table 6
Quality of life measures with the QLS instrument—mean change from baseline to week 30 (LOCF)

QLS measures	Therapy	Baseline		Endpoint		*N*	Change		*p*-Value	
		Mean	S.D.	Mean	S.D.		Mean	S.D.	Within group	vs. Ris
Total score	Olz	72.4	17.9	84.3	22.8	30	11.9	13.4	< 0.001	0.194
	Ris	74.8	16.6	79.7	22.1	26	4.9	19.2	0.203	
Common objects and activities	Olz	6.9	2.5	8.7	2.6	30	1.7	2.6	0.001	0.289
	Ris	7.8	2.2	8.6	2.8	26	0.8	2.3	0.076	
Instrumental role	Olz	15.9	5.0	16.4	5.2	30	0.6	5.5	0.578	0.873
	Ris	15.7	3.7	16.5	3.8	26	0.9	4.4	0.312	
Interpersonal relations	Olz	25.4	9.9	30.1	12.8	30	4.7	8.2	0.004	0.714
	Ris	25.0	8.3	27.8	11.8	26	2.8	10.8	0.190	
Intra-psychic Foundation	Olz	24.2	6.9	29.1	7.7	30	5.0	4.7	< 0.001	0.013
	Ris	26.3	7.4	26.7	8.0	26	0.3	6.2	0.779	

N = number of patients with a baseline and at least one postbaseline measurement; LOCF = last observation carried forward; Olz = olanzapine; Ris = risperidone; QLS = Quality of Life Scale.
Mean baseline values are for all randomized patients with at least one postbaseline measure.

ber of days in hospital was adjusted for exposure to study drugs, the total cumulative days per patient over the whole period (prestudy and study) declined for both groups, with a larger decline in the olanzapine group (data not shown).

For community-based resources, both groups showed a decrease in use of community crisis teams and an increase in home visits. Overall, the olanzapine-treated group showed a larger increase in the use of community-based resources compared to the ris-

Table 7
Quality of life measures with the SF-36 instrument—mean change from baseline to week 30 (LOCF)

SF-36 measures	Therapy	Baseline		Endpoint		*N*	Change		*p*-Value	
		Mean	S.D.	Mean	S.D.		Mean	S.D.	Within group	vs. Ris
Physical functioning	Olz	72.0	26.4	83.0	19.7	32	10.9	21.0	0.006	0.283
	Ris	81.0	22.1	82.8	17.2	30	1.8	13.7	0.471	
RF limitations—physical	Olz	51.6	42.6	68.8	37.0	32	17.2	49.4	0.058	0.202
	Ris	63.3	40.9	59.2	42.3	30	− 4.2	47.4	0.634	
RF limitations—emotional	Olz	36.5	39.1	68.8	41.4	32	32.3	49.0	< 0.001	0.046
	Ris	46.7	44.3	46.7	46.0	30	0.0	58.1	1.00	
Bodily pain	Olz	71.9	25.1	82.4	18.3	32	10.5	25.1	0.025	0.766
	Ris	72.8	31.1	81.6	25.4	30	8.8	22.6	0.041	
General health	Olz	56.7	24.3	65.2	26.7	32	8.4	20.4	0.026	0.355
	Ris	58.7	23.5	60.8	30.7	30	2.1	28.9	0.698	
Vitality total	Olz	44.2	22.2	57.2	20.6	32	13.0	17.8	< 0.001	0.127
	Ris	46.2	24.0	50.5	25.0	30	4.3	28.6	0.414	
Social functioning	Olz	51.2	30.8	69.5	27.5	32	18.4	39.7	0.014	0.603
	Ris	57.5	30.2	68.3	33.6	30	10.8	33.9	0.091	
Mental health	Olz	48.5	24.6	62.1	22.5	32	13.6	23.5	0.003	0.170
	Ris	53.7	24.4	57.7	27.8	30	4.0	25.9	0.405	
Self-reported change	Olz	47.7	27.2	39.1	28.4	32	− 8.6	31.5	0.133	0.515
	Ris	41.7	24.9	41.7	28.1	30	0.0	30.1	1.00	

N = number of patients with a baseline and at least one postbaseline measurement; Olz = olanzapine; Ris = risperidone; LOCF = last observation carried forward; RF = role functioning.
Mean baseline values are for all randomized patients with at least one postbaseline measurement.

peridone-treated group (data not shown). Due to the low level of use of some resources, these differences were not statistically significant.

3.8. Other functional indicators

The olanzapine-treated group showed an increase from baseline to endpoint levels in productive hours per month, while the risperidone-treated group showed a decrease from baseline to endpoint levels in productive hours per month. However, this difference in cumulative mean hours was not statistically significant.

Welfare payments were similar in both groups. At endpoint, mean welfare payments per month had risen in both groups to similar levels.

4. Discussion

This study utilized a protocol similar to a larger double-blind study conducted in Europe and the United States (Tran et al., 1997). It was designed to examine olanzapine and risperidone in terms of efficacy, safety, quality-of-life, and resource-use measures, and thereby contribute toward an understanding of their relative risk:benefit ratio when used in the Australian or New Zealand setting.

Doses used for both agents in this study warrant further comment, as they may be a limitation of this trial. Both drugs were initiated at a relatively high starting dose, which resulted in a higher average daily dose than is likely to occur in a naturalistic setting (Gómez et al., 2000). The risperidone dose schedule was consistent with the approved prescribing information in Australia. Following the recommended dose-titration process, dose was increased to 3 mg b.i.d. by the third day. Investigators were able to titrate the dose within the range of 4 to 8 mg/day, as recommended by the prescribing information at the time of the study. This resulted in a mean modal dose of 6.6 mg/day, higher than frequently reported risperidone doses. It is difficult to determine the significance of this when the study doses were titrated by investigators based on response, and average daily doses reported from audits may include a range of indications and severity of illness. The olanzapine regimen used a starting dose higher than that recommended in the approved prescribing information, but still within the recommended dose range. This dose was used to test the effect on tolerability, especially with regard to EPS. Although investigators were able to adjust the dose within the recommended range of 10 to 20 mg/day, the mean modal dose was 17.2 mg/day. The higher-than-average daily doses of both drugs may be due in part to the reluctance of clinicians to reduce doses from those established at the start of a clinical trial.

Results showed that both agents were effective in reducing the severity of overall psychotic symptoms. The significant improvement from baseline levels across all efficacy measures in a small sample indicates the effectiveness of both products. Olanzapine-treated patients achieved significantly greater improvement in the PANSS total and BPRS total scores, and PANSS general psychopathology subscore than patients treated with risperidone (Table 3). In addition, a significantly greater percentage of olanzapine-treated patients achieved an improvement in PANSS total score of at least 20% over baseline values ($p = 0.01$). No between group differences were observed in terms of improvement in PANSS positive and negative and CGI-Severity scores. Given the small sample size and, therefore, the attenuated power of the statistical comparisons, the significantly greater improvements with olanzapine in the PANSS total and BPRS total scores, and in the PANSS general psychopathology subscore may suggest a useful advantage, especially if accompanied by improvements in tolerability. The observation that more olanzapine-treated patients completed the 30-week period than did risperidone-treated patients (53% vs. 36%, $p = 0.174$) may be further evidence of this relative advantage. The largest contributor to the difference in drop-outs between the groups was lack of efficacy in patients treated with risperidone.

Because of the relatively small sample size, it is possible that artifacts of the randomization process may have contributed to the results. However, the severity of illness between the two groups was similar as there were no significant differences in the baseline scores in patients randomized to the treatment groups. In addition, an analysis of the number of patients with less than, or greater than or equal to, 2 years from first episode by Fisher's Exact test failed to show a significant difference between the two groups ($p = 0.258$). Furthermore, the two groups are similar

in regards to the number of hospitalizations within the last year. Unfortunately, data concerning prior response to antipsychotics is absent, but available data suggest that despite the small sample size, the two groups were similar in the severity and duration of illness.

The overall response rate is broadly similar to that of a larger previously reported head-to-head study (Tran et al., 1997), which reported a significantly greater proportion of olanzapine-treated patients achieving 40% and 50% improvements in PANSS total score in a 28-week trial. That study, like this one, was unable to detect any significant advantage for olanzapine in improving the PANSS negative score. However, it reported a greater improvement for olanzapine-treated patients in the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1989) summary score. A recently published 8-week head-to-head clinical trial comparing olanzapine with risperidone showed no significant differences in any efficacy measure between the two groups at endpoint (Conely and Mahmoud, 2001). It is possible that the longer duration of treatment in this study (30 weeks) and in the Tran study (28 weeks) may have revealed the significant advantage of olanzapine over risperidone in treatment of psychotic symptoms.

The burden of impairment suffered by patients with schizophrenia is attributable to a combination of symptom severity and medication side effects. Therefore, set against the observation of significant differences in efficacy between the two drugs, the evaluation of safety becomes particularly important. In this study, the safety evaluation included the systematic recording of all treatment-emergent adverse events, abnormal laboratory values, and specific measures of EPS using well-validated scales for akathisia and parkinsonism. No treatment-emergent adverse events were reported as occurring significantly more frequently with olanzapine compared with risperidone. Of the three events seen significantly more frequently with risperidone, somnolence may be the most clinically important.

By any of several measures (Barnes Akathisia and Simpson–Angus Scales, spontaneous treatment-emergent adverse events, and use of anticholinergic medication), the olanzapine-treated group showed numerically less EPS-related problems, although the differences were not significant. In a previously reported head-to-head study (Tran et al., 1997) in which 339 patients participated, olanzapine-treated patients reported significantly less EPS. In this earlier comparative study, olanzapine also exhibited an advantage with respect to hyperprolactinemia and sexual dysfunction, outcomes that were not evaluated in the present study. In an open-label, head-to-head study of olanzapine vs. risperidone, a significant increase in akathisia was observed in risperidone-treated patients compared to olanzapine-treated patients (Ho et al., 1999). The 8-week trial comparing olanzapine with risperidone showed no significant differences in scores on any EPS scale between the two groups at endpoint (Conely and Mahmoud, 2001).

Weight gain has been associated with atypical antipsychotics. Although more olanzapine-treated patients reported weight gain than risperidone-treated patients (5 vs. 2) during open-ended questioning, the actual observed mean weight gain was similar. An analysis of maximum weight gained at any time during therapy relative to baseline shows there was a twofold difference in mean maximum gain between the olanzapine and risperidone groups. However, the mean weight gain from baseline to endpoint was not significantly different between the groups (4.9 kg for olanzapine vs. 4.5 kg for risperidone). These data support the investigator's observation that during the study, a small number of olanzapine patients gained significant amounts of weight.

Transient and clinically unimportant increases in AST/SGOT, ALT/SGPT, and CPK were seen more often among olanzapine-treated patients than risperidone-treated patients. This increase in hepatic transaminases is well documented (Beasley et al., 1996) and this study confirms the transient nature of this phenomenon.

The trend towards modest, but potentially clinically useful, differences in favor of olanzapine was continued in the assessment of quality of life. A significant difference in favor of olanzapine over risperidone on the Role Functioning Limitations—Physical and Role Functioning Limitations—Emotional subscale of the SF-36 and the Intrapsychic Foundation category from the QLS suggests a functional improvement gain with olanzapine. Both olanzapine- and risperidone-treated groups showed similar within-group changes from baseline to end-

point on the QLS, but these changes were significant only for the olanzapine group. Tran et al. (1997) also reported significant baseline-to-endpoint improvements in both olanzapine- and risperidone-treated groups in all QLS measures and a significant improvement in QLS Intrapsychic Foundation measures in the olanzapine-treated group. Using the Psychiatric Status You Currently Have Baseline (PSYCH-BASE) tool in an open label study, Ho et al. (1999) reported no significant differences in quality-of-life measurements between olanzapine- and risperidone-treated groups.

The resource utilization data proved very difficult to collect from patients who had discontinued study drug, in spite of best efforts to do so. Data collected on community and outpatient resource use were, therefore, biased against olanzapine given that more risperidone-treated patients discontinued than olanzapine-treated patients. However, the data collected suggest that olanzapine-treated patients were more likely than risperidone-treated patients to shift from the hospital setting to a community setting.

Suggestion of functional improvement was also seen using the measure of hours of productive activity. Overall, there was a larger gain in productive activity with the olanzapine group compared to the risperidone group, which did not reach statistical significance. This is consistent with the findings of the SF-36 quality-of-life instrument, which showed statistically greater limitations on role functioning (emotional subscale) in the risperidone group. Taken together, data collected in olanzapine-treated patients on the quality of life, hospitalization, and use of community-based resources suggest a trend toward a more productive and positive functional outcome, outside of an institutional setting.

In conclusion, both olanzapine and risperidone were safe and effective in reducing psychopathology. In spite of the small sample, olanzapine performed statistically significantly better on the primary efficacy measure (PANSS total score) on some of the secondary efficacy measures (BPRS total and PANSS General Psychopathology), and was temporally associated with fewer adverse events. More patients receiving olanzapine completed the study, and data suggest there may be potential functional and quality-of-life gains as a result of these differences. Our findings, even though on a much smaller sample, complement those of the previously reported head-to-head study (Tran et al., 1997) that compared these two drugs and found a relative advantage for olanzapine.

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