Quality of Life in Schizophrenia: A Multicenter, Randomized, Naturalistic, Controlled Trial Comparing Olanzapine to First-Generation Antipsychotics

Maurício Silva de Lima, M.D., Ph.D.; Jair de Jesus Mari, M.D., Ph.D.; Alan Breier, M.D.; Anna Maria Costa, M.D., Ph.D.; Eduardo Pondé de Sena, M.D., M.Sc.; and Matthew Hotopf, M.D., Ph.D.

Objective: To assess the effectiveness of olanzapine for treating schizophrenia and to assess if olanzapine promotes a better quality of life than first-generation antipsychotics (FGAs).

Method: Multicenter, naturalistic, randomized controlled study, comparing olanzapine with FGAs, at hospitalization and during a 9-month follow-up. Outcome assessors were blind to the allocated drug. The dose of antipsychotic was determined by doctors according to their clinical practice routines. Data collection was performed from April 1999 to August 2001.

Results: 197 patients with DSM-IV–diagnosed schizophrenia were allocated to olanzapine (N = 104) and FGA (N = 93). Patients taking olanzapine showed greater improvements in Positive and Negative Syndrome Scale (PANSS) negative symptoms (mean difference = 2.3, 95% CI = 0.6 to 4.1) and general psychopathology (mean difference = 4.0, 95% CI = 0.8 to 7.2) subscales and fewer incidences of tardive dyskinesia (RR = 2.4, 95% CI = 1.4 to 4.2, $p < .0001$). Olanzapine was also associated with greater improvement in a number of health-related quality-of-life outcomes on the Medical Outcomes Study 36-item Short-Form Health Survey, including physical functioning (mean difference = 6.6, 95% CI = 1.2 to 11.9), physical role limitations (mean difference = 13.7, 95% CI = 3.0 to 24.3), and emotional role limitations (mean difference = 12.1, 95% CI = 0.7 to 23.5). Patients taking olanzapine gained significantly more weight during the trial than patients taking FGAs, with a correspondent endpoint increase in the body mass index (BMI) of 28.7 versus 25.3 ($p < .001$).

Conclusion: Compared with FGAs, olanzapine has advantages in terms of improvements of negative symptoms and quality of life. It is also associated with fewer incidences of tardive dyskinesia and greater increases in weight and BMI. These findings are highlighted by the naturalistic approach adopted in this trial.

(J Clin Psychiatry 2005;66:831–838)

Received Sept. 20, 2004; accepted Dec. 1, 2004. *From Eli Lilly Brazil, São Paulo, Brazil (Drs. de Lima and Costa); the Federal University of Pelotas and Catholic University of Pelotas, Pelotas, Brazil (Dr. de Lima); Department of Psychiatry, Federal University of São Paulo, São Paulo, and Catholic University of Pelotas, Pelotas, Brazil (Dr. Mari); Eli Lilly and Company, Indianapolis, Ind. (Dr. Breier); Department of Psychiatry, Federal University of São Paulo, São Paulo, Brazil (Dr. Costa); Department of Pharmacology, Federal University of Bahia, Salvador, Brazil (Dr. de Sena); and Guy's King's and St. Thomas' School of Medicine and Institute of Psychiatry, King's College, London, United Kingdom (Dr. Hotopf). Dr. Costa is now with Bristol-Myers Squibb Brazil, São Paulo, Brazil.*

This study was funded by Eli Lilly Brazil, São Paulo, Brazil.

Presented at the 156th meeting of the American Psychiatric Association in San Francisco, Calif., 2003, as a poster, and at the 27th annual meeting of the Nordic Psychiatric Congress in Reykjavik, 2003.

Dr. Mari has received grant/research support from Eli Lilly Brazil. Dr. de Sena has participated in speakers/advisory boards for Eli Lilly Brazil. Drs. de Lima, Breier, Costa, and Hotopf report no other affiliation or financial relationship relevant to the article.

Corresponding author and reprints: Maurício Silva de Lima, M.D., Ph.D., Federal University of Pelotas and Catholic University of Pelotas, Av. Duque de Caxias, 250. Pelotas, RS–Brazil (e-mail: limama@lilly.com).

First-generation antipsychotics (FGAs) are effective in alleviating positive symptoms; however, many patients continue to experience negative symptoms as manifested by reduced functioning and well-being. In addition, these drugs are associated with movement disorders and other serious side effects, which contribute to drug intolerance and poor compliance, increasing the probability of relapse. It has been claimed that second-generation antipsychotics (SGAs) like olanzapine are, in general, more likely to promote improvement in negative symptoms and also to be better tolerated by patients than FGAs.[1] Results from systematic reviews on the efficacy of SGAs suggest these drugs have equivalent efficacy in alleviating positive symptoms as compared with FGAs; whether there are real differences in the efficacy of SGAs and FGAs for the treatment of negative symptoms remains dubious.[2–5] SGAs in general have advantages over FGAs in terms of side effects (in particular extrapyramidal) and attrition rates in randomized controlled trials (RCTs). However, a systematic review using meta-regression revealed, when FGAs are used in low doses (≤ 12 mg/day of

haloperidol or equivalent), they might be equivalent to SGAs even in these aspects.[6]

Health-related quality of life is the value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy.[7] Quality-of-life measures have been only recently used to assess drug treatments in clinical trials. A bibliographic study has estimated that less than 5% of all RCTs reported on quality of life.[8] In trials assessing the value of antipsychotic drugs, it is of particular interest if there are differences between FGAs and SGAs in side effect profiles and/or negative symptoms; do these translate into differences in quality of life?

The assessment of relevant outcomes like quality of life may be impractical within the context of traditional RCTs. Assessment of effects used to be based on biologically meaningful criteria, and the choice of patients and clinical outcomes is rather arbitrary.[9] As a result, extrapolating results from these trials to standard clinical conditions is often complicated. Pragmatic trials, an alternative to the traditional RCTs, aim to answer "real-life" clinical questions in "real-life" clinical situations. There is a need to look at "real-life" clinical situations using pragmatic designs with adequate follow-up, as opposed to looking at the highly selected samples of patients in most RCTs.

We present results from a pragmatic RCT of olanzapine versus FGAs in Brazil, which aimed to assess symptom change, side effects, and quality of life in patients with schizophrenia.

METHOD

Study Design

This was a naturalistic multicenter RCT comparing olanzapine with FGAs in patients with DSM-IV[10] schizophrenia. Patients aged 18 to 55 years admitted to psychiatric hospitals with an acute exacerbation of their illness were included in this study. The study protocol was approved by the institutional review boards responsible for the individual study sites and by the Federal University of São Paulo ethical committee. Data collection was performed from April 1999 to August 2001.

Sites

The study was conducted in 3 psychiatric hospitals from different cities and regions in Brazil: Anna Rech (southern Brazil), Salvador (northeastern Brazil), and Goiânia (midwestern Brazil).

All psychiatrists and psychologists who participated in the trial were trained to the clinical and research procedures according to a protocol. In the site initiation, it was emphasized that this was a naturalistic study, and the aim was to have doctors acting as closely as possible to their general practice attitudes.

Inclusion and Exclusion Criteria

Patients were eligible if they were admitted to a psychiatric unit with a diagnosis of schizophrenia and a minimal Brief Psychiatric Rating Scale[11] (extracted from Positive and Negative Syndrome Scale [PANSS][12]) score of 24. They were required to be living with a relative in an area within 60 km from the hospital, in order to allow follow-up visits in the same inpatient facility and with the same doctor. Informed consent was obtained from all eligible subjects or from their authorized legal representatives. Patients with serious suicidal risk, patients with physical illness (such as cancer or severe hepatic disease), female patients who were either pregnant or lactating, and patients who had received treatment with any SGA in the previous 4 weeks were excluded.

Sample Size Calculation

A 20% dropout rate was assumed, for an estimated level of significance of 5% and a statistical power of 80%. Estimated prevalences for the main efficacy outcomes—mean changes in PANSS and in Medical Outcomes Study 36-item Short-Form Health Survey (SF-36)[13] at end of study—were obtained. Quality-of-life measures were intended to detect a 10% mean difference between groups. The resulting final needed number of patients in each group was 100.

Randomization

Randomization was performed centrally: after baseline assessment of each patient, investigators received sealed, numbered, coded envelopes, which described the treatment to be given to the patient, from a person who had no contact with the patient's evaluation. This procedure aimed to guarantee adequate allocation concealment.

Blindness

We aimed to replicate normal clinical practice as far as possible, so patients and clinicians were not blind to the treatment allocated. The open design allowed doses of treatments to be manipulated as the investigator chose. However, in order to prevent observer bias, the main efficacy assessments were performed by interviewers (psychiatrists and psychologists) who were masked to treatment allocation and had no contact with the treating doctors or the patients' hospital records. The criterion for choosing this interview team was basically that the person should have little or no contact with the inpatient unit where study patients were assessed and treated. Because of sites' routines, it was possible to guarantee that raters who were psychiatrists (at sites in Ana Rech and Salvador) worked in different units, particularly with drug abuse/dependence services, than the investigators. Raters who were psychologists (Goiânia) worked at different periods than the investigators. No rater had team

meetings in which patients' status was discussed and/or responsible psychiatrists attended.

Treatment

Eligible patients were randomly assigned within a maximum period of 3 days after hospital admission. The psychiatrists responsible for hospitalization determined the daily dose of the allocated drugs as adopted in their clinical practice routines. According to patients' clinical improvement and/or emergent side effects, doses could be adjusted upward or downward. In case of allocation to the FGA group, psychiatrists were also instructed to choose the drug according to the patient's characteristics and the psychiatrist's own clinical practice procedures. The psychiatrists were free to decide if concomitant medications should be prescribed in conjunction with olanzapine or FGAs. As this was a "real world" study, concomitant therapy was allowed, including benzodiazepines and anticholinergic medications, among others. Prophylactic use of anticholinergic medication was discouraged although not proscribed. All other interventions used in the period of the study were recorded and analyzed.

After discharge, patients were followed up for 9 months, at monthly intervals, at the same inpatient facility and under care of the same doctors. Treatment adherence was assessed by asking patients to bring their medicine boxes in order to count the number of pills used in the preceding period. In case the patient did not return for consultation, he or she was contacted to reschedule the visit. If the patient did not attend at the second recall, a trained research worker visited the patient at home.

Outcomes

Efficacy assessments. The main outcomes of the study are reported in this article: results on the PANSS, the Clinical Global Impressions scale (CGI), and the SF-36 and clinical response (at least a 40% reduction from baseline values in PANSS total score). Relapse was recorded when patients had to be rehospitalized because of illness-related factors.

Safety assessments. Adverse events were recorded at every visit, including entry (visit 0) and randomization (visit 1), through nondirected, open-ended questioning, spontaneous complaint, and clinical observation. Adverse events were recorded monthly during follow-up (outpatient period) irrespective of their potential relationship to treatment. In addition, the Abnormal Involuntary Movement Scale for Tardive Dyskinesia (AIMS)[14] was used. The AIMS scale comprises 12 items. The first 7 items assess specific abnormal movements (face, lips, jaws, tongue, upper extremities, lower extremities, and trunk), scored on a 5-point scale (0 for none/normal to 4 for severe).

Quality-of-life assessment. Quality of life was evaluated using the SF-36, a generic health status measure designed to evaluate functioning and well-being in chronic disease, mental health specialty, and general primary care populations.[13] The SF-36 consists of 36 questions covering 8 domains: physical functioning, bodily pain, role limitations due to physical problems, vitality, general health perceptions, role limitations due to emotional problems, mental health, and social function. Each subscale is linearly transformed into a 0 to 100 scale, with higher scores representing better health status and functioning. The SF-36 subscales have excellent reliability and good construct validity.[15]

Analysis

We analyzed continuous variables by analysis of covariance, for which the dependent variable was the score at the endpoint, and the independent variables were treatment group and baseline score. The results are presented as the corrected mean differences between the treatment groups, with their respective 95% confidence intervals. Because data at the endpoint were not complete due to dropouts, we used 3 strategies in the analysis: (1) endpoint analysis, for which only those patients with complete data at endpoint were included; (2) last observation carried forward, for which missing values were substituted with the last observation (which for many endpoints was, in fact, the observation at baseline); and (3) imputation, using the impute command of STATA, for which missing values are imputed on the basis of baseline values, gender, and age of participants.

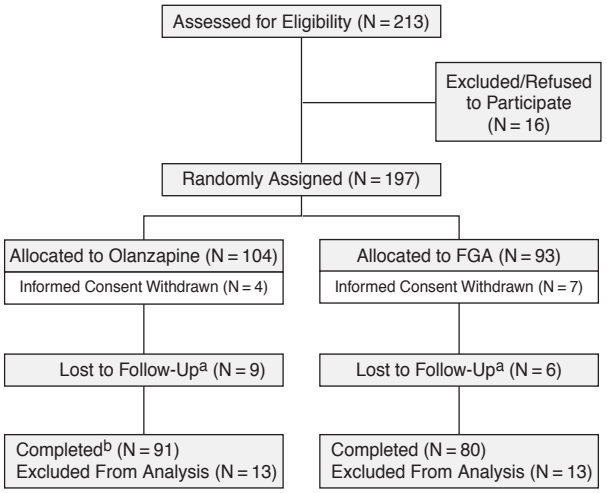
Dichotomous data, including demographic variables, response rates (defined as at least a 40% reduction in total PANSS scores from baseline to end of study), reasons for treatment discontinuation, and treatment-emergent adverse events, were evaluated using Pearson χ^2 test, with relative risks and their respective 95% confidence intervals being obtained. Wherever possible, the efficacy analysis was based on the intention-to-treat principles, i.e., all randomly assigned patients were considered, assuming that dropouts occurred because of lack of efficacy or adverse events. The adopted level of significance was 5%.

We entered the site of the study into each of the models to determine whether controlling for this altered our main findings. We also examined whether there were any interactions between site and randomization group.

RESULTS

A total of 197 patients (154 males and 43 females) were recruited. The process of recruitment and follow-up is described in the CONSORT diagram (Figure 1).[16] The number of patients in each treatment group is not exactly equal (52% in the olanzapine group and the remaining 48% in the FGA group), which can occur by chance, and overall the distribution was similar, allowing comparisons between groups.

Figure 1. Participant Flow



[a]All patients who discontinued the study because of known reasons like pregnancy, adverse events, or protocol violation were counted as lost to follow-up.
[b]For continuous variables. Regarding binary variables, all randomly assigned patients were considered (intention-to-treat analysis).
Abbreviation: FGA = first-generation antipsychotic.

Baseline Characteristics

Treatment groups did not differ on an overall basis statistically significantly with respect to any patient or illness characteristic. Participants were generally in their mid-30s, male, white, and unmarried. The mean length of illness was about 11 years, and mean age at onset was 22 years (Table 1).

The mean (SD) baseline scores on the PANSS were 48.3 (12.7) for general psychopathology, 27.1 (7.5) for positive symptoms, and 26.1 (7.4) for negative symptoms (total mean score = 101.5 [23.2]), indicating this was a population with severe overall psychopathology. Thus, this overall patient group manifested a clinically severe illness in the context of a chronic longitudinal course.

Medication Use

Mean and median maximum drug dosages during trial were calculated for patients who completed at least 3 visits (baseline assessment, randomization visit, and discharge). The mean (SD) dose of olanzapine was 10.5 mg/day (2.5 mg/day) and a median 10 mg/day. Haloperidol was the most frequently prescribed FGA, used on 74 patients, with a mean dose of 15.8 mg/day (23.7 mg/day) and a median 10 mg/day. Chlorpromazine was used in 13 patients at a mean dose of 346.2 mg/day (150.6 mg/day) with a median dose of 300 mg/day. Trifluoperazine was used in 1 patient at a dose of 15 mg/day.

During hospitalization, concomitant medication was prescribed for 49.5% of patients taking olanzapine and for 69.4% of those taking FGAs (Pearson $\chi^2 = 7.4$, df = 1, p = .006). This difference favoring olanzapine was similarly observed at the end of the follow-up (48.3 vs. 65.3%; RR = 1.5, 95% CI = 1.0 to 2.1, p = .02). The most prescribed medications were benzodiazepines for participants taking olanzapine (16.5%) and anticholinergic drugs for those taking FGAs (26.3%).

Adherence to prescribed medication was high for both groups at end of trial: 92.1% for olanzapine and 90.7% for the FGA group (p = .79).

Attrition Rate

The overall discontinuation rate during trial was 13.2%, with no statistically significant differences between groups. The main reasons for dropouts are shown in Table 2. The main reason for dropping out of the trial was lack of efficacy.

Efficacy Analysis

Results of the PANSS are shown in Table 3. There was no difference between treatment groups in positive symptoms at follow-up. Patients treated with olanzapine had slightly lower negative symptom, general psychopathology, and total scores on the PANSS. The alternative methods we used to deal with missing data did not alter these findings.

Clinical Response and Relapse Rates

Clinical response as measured by a reduction of at least 40% in the PANSS baseline scores revealed no statistically significant differences among both groups (46% reduction for olanzapine and 35% reduction for FGAs [$\chi^2 = 2.01$, df = 1, p = .19]).

Relapse was more frequently observed among patients taking FGAs (45.6% vs. 28.4%), a statistically significant difference (RR = 1.4, 95% CI = 1.1 to 1.9).

Quality-of-Life Results

Results on the SF-36 are displayed in Table 4. Patients treated with olanzapine reported statistically significantly improved physical functioning, physical role limitations, and emotional role limitations compared with those receiving FGAs. The alternative approaches we used to deal with missing data did not make major differences in these findings.

We tested for the effect of site on treatment response and did not find any differences between the 3 sites in terms of the main outcome measures (SF-36 and PANSS). There were no interaction terms between treatment and site on these measures.

Acceptability Results

No patients taking FGAs left the study early because of side effects, which may be related to the naturalistic approach adopted in this trial, allowing clinicians to prescribe lower doses of FGAs and also to add other

Table 1. Demographic Characteristics of Patients With Schizophrenia Treated With Olanzapine or FGAs

	Olanzapine (N = 104)		FGAs (N = 93)		Analysis		
Characteristic	N	%	N	%	χ^2	df	p Value
Diagnosis (subtype)							
Paranoid	64	61.5	57	61.3	14.18	10	.165
Residual	16	15.4	6	6.5			
Schizoaffective	12	11.5	9	9.7			
Others	11	10.6	21	22.3			
Site							
Anna Rech	60	57.7	53	57.0	0.09	2	.957
Goiânia	25	24.0	24	25.8			
Salvador	19	18.3	16	17.2			
Gender, male	78	75.0	76	81.7	0.87	1	.352
Race[a]							
Caucasian	65	64.4	57	61.3	0.79	2	.671
African descent	22	21.8	18	19.4			
Other	14	13.7	17	18.3			
Marital status, not married	89	85.6	73	78.5	2.14	1	.144
	Mean	SD	Mean	SD	t Test	df	p Value
Age, y	34.05	8.84	33.52	8.66	0.17	1	.679
Length of illness, y	11.60	8.82	10.92	7.11	0.32	1	.572
Age at onset, y	22.03	6.82	22.78	7.92	0.47	1	.492

[a]Subtotals vary due to sporadic missing data.
Abbreviation: FGAs = first-generation antipsychotics.

Table 2. Disposition of Patients With Schizophrenia Treated With Olanzapine or FGAs

	Olanzapine (N = 104)		FGAs (N = 93)		
Status	N	%	N	%	p Value
Completed	91	87.5	80	86.0	.385
Discontinued: reason					
Informed consent withdrawn[a]	4	3.8	7	7.5	
Adverse event	1	1.0	0	0.0	
Protocol violation	0	0.0	1	1.1	
Pregnancy	0	0.0	1	1.1	
Lost to follow-up	8	7.7	4	4.3	

[a]Occurred during the first phase of the study (hospitalization).
Abbreviation: FGAs = first-generation antipsychotics.

medications, such as anticholinergic agents. In the olanzapine group, only 1 patient dropped out because of side effects.

In relation to weight gain, the mean body mass index (BMI) was 25.5 for olanzapine and 23.4 for the FGA group at baseline. After 9 months, the mean BMI for olanzapine was 28.7 and 25.3 for the FGA group, a statistically significant difference ($F = 224.3$, $p < .001$). There was, therefore, a BMI increase for those taking olanzapine treatment.

At the end of the trial, all AIMS main components were statistically significant in favor of olanzapine over FGAs. Table 5 shows the analysis carried out by grouping rates in global assessment, taking scores 0 (none), not presenting an abnormal movement at all, and 1,2,3,4 as presenting some degree of the condition. The incidence of tardive dyskinesia was 10 (11.5%) of 87 patients for olanzapine and 28 (38.9%) of 72 patients for FGA treatment (RR = 0.4, 95% CI = 0.2 to 0.7, $p < .0001$). Other items of the AIMS also indicated that olanzapine is associated with fewer incidences of extrapyramidal symptoms than FGAs.

DISCUSSION

Main Findings

This is the first RCT comparing olanzapine to FGAs conducted under "real-life" conditions, in 3 distinct urban Brazilian cities. The use of olanzapine was associated with improved negative symptomatology and general psychopathology on the PANSS. Olanzapine was also better tolerated, with patients taking olanzapine showing lower rates of extrapyramidal symptoms than patients taking FGAs, although the increase in BMI was significantly higher among those taking olanzapine. The use of olanzapine had a major impact on health-related quality of life, as measured by the SF-36. The significant findings in differential quality-of-life improvements in patients taking olanzapine versus patients taking FGAs were related to the physical components such as physical functioning and physical role limitations.

Traditional RCTs vs. Pragmatic Trials

Because we aimed to study the "real-world" consequences of selecting an antipsychotic drug rather than the clinical efficacy under ideal conditions, this trial was conducted under the conditions of routine psychiatric care in Brazil. Its design incorporated a number of features to increase generalizability to "real-world" practice. In order

Table 3. Change From Baseline to Endpoint (9 months after discharge) in Mean (SD) PANSS Severity of Illness Scores of Patients With Schizophrenia Treated With Olanzapine or FGAs[a]

	Olanzapine				FGAs				Endpoint Score[b]					
	Baseline, N = 100		Endpoint, N = 87		Baseline, N = 90		Endpoint, N = 74		Completers			LOCF[b]		
Variable	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean	(SD)	Mean Difference	CI	p	Mean Difference	CI	p
Positive symptoms	28.1	(7.3)	14.8	(6.8)	26.1	(7.6)	14.9	(7.9)	0.8	–1.2 to 2.9	.4	1.2	–1.0 to 3.4	.3
Negative symptoms	26.1	(7.3)	19.6	(6.1)	26.0	(7.6)	22.1	(7.5)	2.4	0.5 to 4.3	.014	2.3	0.6 to 4.1	.009
General psychopathology	49.5	(19.9)	31.6	(11.3)	46.8	(12.4)	34.0	(12.5)	3.6	0.4 to 6.9	.027	4.0	0.8 to 7.2	.016
Total PANSS	103.7	(22.8)	65.9	(21.7)	98.8	(23.5)	71.1	(25.8)	7.2	0.6 to 13.7	.03	7.7	1.14 to 14.3	.02

[a]Subtotals vary due to sporadic missing data.
[b]Corrected for baseline values by analysis of covariance (positive values favor olanzapine).
Abbreviations: FGAs = first-generation antipsychotics, LOCF = last observation carried forward, PANSS = Positive and Negative Syndrome Scale.

Table 4. Change From Baseline to Endpoint (9 months after discharge) in Mean SF-36 Scores of Patients With Schizophrenia Treated With Olanzapine or FGAs[a]

	Olanzapine		FGAs		Endpoint[b]					
	Baseline,	Endpoint,	Baseline,	Endpoint,	Completers			LOCF[c]		
Variable	N = 99	N = 84	N = 91	N = 72	Mean Difference	CI	p	Mean Difference	CI	p
Physical functioning	65.1	82.3	67.1	73.8	8.2	1.6 to 14.8	.015	6.6	1.2 to 11.9	.017
Role physical	34.4	58.1	32.3	40.0	17.7	5.5 to 29.9	.005	13.7	3.0 to 24.3	.012
Bodily pain	70.0	86.0	67.6	79.1	6.1	–1.54 to 13.8	.12	6.1	–1.5 to 13.8	.12
General health	57.1	67.0	59.3	61.1	6.4	–0.4 to 13.1	.06	5.6	0.0 to 11.3	.05
Vitality	48.6	56.3	44.5	51.0	2.0	–4.4 to 8.4	.5	0.4	–5.1 to 5.9	.9
Social functioning	48.0	72.2	53.9	67.1	5.7	–3.0 to 14.5	.2	5.4	–2.3 to 13.2	.17
Role emotional	30.8	58.4	31.8	42.1	15.8	2.7 to 30.0	.02	12.1	0.7 to 23.5	.04
Mental health	50.5	64.0	50.9	58.1	5.7	–0.5 to 11.9	.07	5.1	–0.3 to 10.4	.06

[a]Subtotals vary due to sporadic missing data.
[b]Corrected for baseline values by analysis of covariance (positive values favor olanzapine).
[c]LOCF means missing values are replaced by baseline scores.
Abbreviations: FGAs = first-generation antipsychotics, LOCF = last observation carried forward, SF-36 = Medical Outcomes Study 36-item Short-Form Health Survey.

Table 5. Risk of Presenting an Abnormal Involuntary Movement After 9-Month Treatment With Olanzapine (N = 87) or FGAs (N = 72)[a]

AIMS Item	Olanzapine, N (%)	FGAs, N (%)	RR (95% CI)	p Value
Tardive dyskinesia	10 (11.5)	28 (38.9)	0.4 (0.2 to 0.7)	< .001
Incapacitation	20 (23.0)	34 (47.2)	0.6 (0.4 to 0.8)	.001
Patient awareness	16 (18.4)	25 (34.7)	0.6 (0.4 to 1.0)	.015
Choreoathetosis	0 (0.0)	9 (12.5)	*	.001
Dystonia	5 (5.7)	15 (20.8)	0.4 (0.2 to 0.9)	.004

[a]Subtotals vary due to sporadic missing data.
*Not possible to calculate because 1 of the cells is 0.
Abbreviations: AIMS = Abnormal Involuntary Movement Scale, FGAs = first-generation antipsychotics.

to enroll a representative sample of patients currently treated in Brazilian psychiatric settings, relatively few restrictions were placed on eligibility. After random assignment of initial treatment, dose adjustments and use of concomitant medications were managed as usual by the psychiatrists, which can partially explain the low dropout rate observed in this study for both groups. It can be assumed that these design features, instead of addressing questions related to efficacy, do provide answers to questions about treatment effectiveness, in this case, how the choice of an antipsychotic can positively affect relevant outcomes, including improvements in negative symptoms and quality of life in "real-world" practice.

Usually, findings from pragmatic trials are not generalizable to health care systems with different prescribing patterns, physician training, or constraints on the use of health resources. However, this multicenter trial had the advantage of being representative of 3 very distinct local systems and practices. Testing interaction terms for setting did not result in any substantial changes for the main outcome measures, which highlights the broad applicability of these findings.

Efficacy Findings

Compared with FGAs, olanzapine showed better results in a number of efficacy outcomes. Differences from baseline in PANSS subscales indicated that olanzapine has similar efficacy in positive symptoms and clinical response (at least a 40% reduction from baseline in PANSS total score) and superior efficacy in both negative symp-

toms and general psychopathology and in PANSS total scores. Also, the relapse rate was higher for patients taking FGAs, and more patients taking olanzapine had scores of 0 (healthy), 1 (much better), or 2 (better) on the CGI scale at visit 11. This superior efficacy profile of olanzapine has been found in other RCTs in which it was compared with FGAs.[17–20] Recently, a systematic review and meta-analysis has addressed the issue of the efficacy of SGAs, particularly looking at differences among these drugs when compared with FGAs.[21] Findings suggest SGAs cannot be considered as a homogeneous group, and olanzapine, clozapine, risperidone, and amisulpride have superior efficacy to FGAs, regardless of haloperidol dose (or all FGA comparators converted to haloperidol-equivalent doses).

Olanzapine was shown to be associated with a marked improvement in 3 domains of the SF-36 (physical functioning, physical role limitations, and emotional role limitations). Since mean differences from baseline at the end of trial were higher in all domains in patients taking the SGA drug, lack of statistical power could explain the absence of significance for the remaining domains of the scale. Interestingly, the endpoint scores on the SF-36 in patients taking olanzapine were quite similar to those observed in the general population in the United States.[22] Although this is not a direct comparison, it could be assumed that patients taking olanzapine might achieve clinically relevant health-related quality-of-life improvements. Data on quality of life have been investigated in another olanzapine trial,[19] but it is difficult to compare the magnitude of that data to the current study. According to a Cochrane review,[3] these trials did not fully report recorded quality-of-life data, and, when reported, the data were presented in a form impossible to summarize in a meta-analysis.

Acceptability/Side Effects

Although most of the trials have found that olanzapine is associated with a lower rate of dropouts because of side effects, in some studies, no statistically significant differences between olanzapine and FGAs were found for this outcome.[23–25] In this trial, it is likely that the naturalistic approach adopted allowed psychiatrists to use their routine strategies to keep patients in treatments, using lower doses or adding other medications. This could explain why no dropouts because of side effects were observed among patients taking FGAs.

The advantage of olanzapine in terms of extrapyramidal effects observed in this trial is a general finding in other studies that compared this drug with FGAs.[2,20,24] This lower incidence of extrapyramidal side effects, as associated with some degree of improvements in negative symptoms,[26] could also partially explain the higher scores in some components of the SF-36 among those taking olanzapine.

The greater increase in weight and BMI among those taking olanzapine is well known. However, it is suggested that the mean weight gain during olanzapine treatment trended toward a plateau after the initial 39 weeks of treatment with no further significant gain out to 3 years.[27] Although in this trial no dropouts occurred because of weight gain, and notably patients taking FGAs also had significant increase in their BMI after 9 months, further research is needed to assess the relative medical risk that occurs as a consequence of weight gain associated with use of atypical antipsychotics.[28] The simple and pragmatic approach adopted in this trial did not have the benefits of a full range of laboratory examinations that could impact the actual risk of patients taking antipsychotics in terms of glucose abnormalities, as well as dyslipidemias.

Limitations

Randomized controlled trials have been considered the gold standard for efficacy assessment of interventions. Their internal validity is strong, but generally these trials are conducted under ideal conditions. Usually, professionals involved in a trial are atypical, often with a special interest in the problem. Second, it is often difficult to recruit subjects to RCTs, and the patients included are often unrepresentative of the clinical problem.[29] We used the CONSORT diagram, and our results suggest that the less restrictive criteria adopted for including patients in this trial resulted in a low proportion of patients assessed but not actually randomly assigned.

The standard RCT's features may constitute a problem when the aim is putting evidence into clinical practice. Clinicians generally want to know about the external validity or generalizability of a trial, in other words, if the trial's results apply to their clinical practice.

Randomized clinical trials often have a long list of exclusion criteria, but because clinicians need to apply the results of the trial to their own circumstances, they want trials to include broader groups of subjects. In this study, we included all subjects with schizophrenia regardless of other psychiatric comorbidities, and although we excluded individuals with serious medical comorbidities, this was, in effect, a small proportion of patients (Figure 1). Also, subjects were selected from very distinct regions in Brazil, presenting some differences in their sociodemographic characteristics, which increases the generalizability of our data.

Because this study was a pragmatic trial, it was not double-blinded. When blindness is kept during a trial, it is expected that both doctors' and patients' expectations for treatment groups would not induce bias because they are not aware of treatment allocation. Also, observer bias could occur, as the knowledge of the observer affects the way in which he or she scores an outcome. However, in drug trials, it is difficult to maintain blindness for all these levels (patients and doctors/observers), particularly for

long periods of follow-up. In this study, we did not use a double-blind approach, but we kept those responsible for efficacy assessments at baseline, discharge, and endpoint blinded to treatment allocation.

If RCTs are to help in deciding upon which interventions to use, they must be applied to simple and important clinical questions and must be carried out, as far as possible, under the usual service conditions of our health service. This randomized naturalistic trial has the advantage of balancing the generalizability of an observational study against the internal validity of RCTs. This balance was obtained mainly through an adequate randomization and allocation concealment procedure.

Pragmatic trials should compare new treatments with relevant comparisons. We believe our results suggest this was the case in this investigation. Patients treated with FGAs also improved in most of the efficacy outcomes and had low dropout rates as observed in this study. Low dropout rates are an essential feature of this trial, since high follow-up rates improve the internal validity of an RCT.

Drug names: chlorpromazine (Thorazine, Sonazine, and others), clozapine (Clozaril, FazaClo, and others), haloperidol (Haldol and others), olanzapine (Zyprexa), risperidone (Risperdal), trifluoperazine (Stelazine and others).

REFERENCES

1. Tran PV, Dellva MA, Tollefson GD, et al. Extrapyramidal symptoms and tolerability of olanzapine versus haloperidol in the acute treatment of schizophrenia [Published correction appears in J Clin Psychiatry 1997;58:275]. J Clin Psychiatry 1997;58:205–211
2. Duggan L, Fenton M, Dardennes RM, et al. Olanzapine for schizophrenia. In: The Cochrane Library, Issue 2, 2003. Chichester, England: Wiley
3. Kennedy E, Song F, Hunter R, et al. Risperidone versus typical antipsychotic medication for schizophrenia. In: The Cochrane Library, Issue 2, 2003. Chichester, England: Wiley
4. Srisurapanont M, Disayavanish C, Taimkaew K. Quetiapine for schizophrenia. In: The Cochrane Library, Issue 2, 2003. Chichester, England: Wiley
5. Wahlbeck K, Cheine M, Essali MA. Clozapine versus typical neuroleptic medication for schizophrenia. In: The Cochrane Library, Issue 2, 2003. Chichester, England: Wiley
6. Geddes J, Freemantle N, Harrison P, et al. Atypical antipsychotics in the treatment of schizophrenia: systematic overview and meta-regression analysis. BMJ 2000;321:1371–1376
7. Patrick DL, Erickson P. Assessing health-related quality of life for clinical decision-making. In: Walker SR, Rosser RM. Quality of Life Assessment. London, UK: Kluwer Academic Publishers; 1993:11–63
8. Sanders C, Egger M, Donovan J, et al. Reporting on quality of life in randomised controlled trials: a bibliographic study. BMJ 1998;317: 1191–1194
9. Schwartz D, Lellouch J. Explanatory and pragmatic attitudes in therapeutical trials. J Chronic Dis 1967;20:637–648
10. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
11. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
12. Kay SR, Fiszbein A, Opler LA. The Positive and Negative Syndrome Scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–276
13. Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36), 1: conceptual framework and item selection. Med Care 1992;30:473–483
14. Guy W, ed. Abnormal Involuntary Movement Scale (AIMS). In: ECDEU Assessment Manual for Psychopharmcology, revised. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:534–537
15. Revicki DA. Methods of pharmacoeconomic evaluation of psychopharmacologic therapies for patients with schizophrenia. J Psychiatry Neurosci 1997;22:256–266
16. Moher D, Schulz KF, Altman D. The CONSORT statement: revised recommendations for improving the quality of reports of parallel-group randomized trials. JAMA 2001;285:1987–1991
17. Beasley CM Jr, Sanger T, Satterlee W, et al. Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacology (Berl) 1996;124:159–167
18. Conley RR, Tamminga CA, Bartko JJ, et al. Olanzapine compared with chlorpromazine in treatment-resistant schizophrenia. Am J Psychiatry 1998;155:914–920
19. Tollefson GD, Beasley CM, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997;154:457–465
20. Jakovljevic M, Dossenbach MRK, Friedel, P, et al. Olanzapine versus fluphenazine in the acute (six-week) treatment of schizophrenia. Psychiatr Danub 1999;11:3–10
21. Davis J, Chen N, Glick ID. A meta-analysis of the efficacy of second-generation antipsychotics. Arch Gen Psychiatry 2003;60:553–564
22. Tunis SL, Croghan TW, Heilman DK, et al. Reliability, validity, and application of the Medical Outcomes Study 36-item Short-Form Health Survey (SF-36) in schizophrenic patients treated with olanzapine versus haloperidol. Med Care 1999;37:678–691
23. Beasley CM Jr, Dellva MA, Tamura RN, et al. Randomized, double-blind comparison of the incidence of tardive dyskinesia during long-term treatment with olanzapine or haloperidol. Br J Psychiatry 1999;174:23–30
24. Mraz K, Gogus A, Tunca Z, et al. Olanzapine versus chlorpromazine in Turkey [abstract]. Schizophr Res 2000;41:190
25. Loza N, El-Dosoky AM, Okasha TA, et al. Olanzapine compared to chlorpromazine in acute schizophrenia. Eur Neuropsychopharmacol 1999;9(suppl 5):S291
26. Tollefson GD, Sanger TM. Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. Am J Psychiatry 1997;154:466–474
27. Kinon BJ, Basson BR, Gilmore JA, et al. Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia. J Clin Psychiatry 2001;62:92–100
28. Lieberman JA, Tollefson G, Tohen M, et al. Comparative efficacy and safety of atypical and conventional antipsychotics drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. Am J Psychiatry 2003;160:1396–1404
29. Hotopf M, Churchill R, Lewis G. Pragmatic randomised controlled trials in psychiatry. Br J Psychiatry 1999;175:217–223