The Safety of Olanzapine Compared With Other Antipsychotic Drugs: Results of an Observational Prospective Study in Patients With Schizophrenia (EFESO Study)

Juan Carlos Gómez, M.D.; José Antonio Sacristán, M.D.; Jesús Hernández, M.D.; Alan Breier, M.D.; Patricio Ruiz Carrasco, M.D.; César Antón Saiz, M.D.; and Eva Fontova Carbonell, M.D., for the EFESO Study Group

Introduction: Results of controlled clinical trials should be confirmed through safety and effectiveness studies in nonselected patient cohorts treated according to routine clinical practice.

Method: Outpatients with schizophrenia (ICD-10 criteria) entered this prospective, naturalistic study when they received a new prescription for an antipsychotic drug. Treatment assignment was based on purely clinical criteria, as the study did not include any experimental intervention. Safety was evaluated through the collection of spontaneous adverse events and a specific questionnaire for extrapyramidal symptoms. Global clinical status was measured through the Clinical Global Impressions-Severity (CGI-S) and the Global Assessment of Functioning (GAF) scales.

Results: From the 2967 patients included, 2128 patients were treated with olanzapine as monotherapy or combined with other drugs (olanzapine group), and 821 were treated with other antipsychotic drugs as monotherapy or combined with other drugs (control group). There were no statistical differences between treatment groups at baseline regarding age, gender, disease duration, or severity of symptoms. Olanzapine was well tolerated and effective in this study. Overall incidence of adverse events was significantly lower in the olanzapine group compared with the control group ($p < .001$). Somnolence and weight gain were significantly more frequent in the olanzapine group, and akathisia, dystonia, extrapyramidal syndrome, hypertonia, hypokinesia, and tremor were significantly higher in the control group. Clinical improvement at endpoint, measured through the mean change in the CGI-S and the GAF, was significantly higher in the olanzapine group compared with the control group ($p = .004$).

Conclusion: These results show that olanzapine is safe and effective in nonselected schizophrenic outpatients and are consistent with the efficacy and safety profile that olanzapine has shown in previous controlled clinical trials.

(J Clin Psychiatry 2000;61:335–343)

Received Sept. 3, 1999; accepted Dec. 30, 1999. From Eli Lilly and Company, Madrid, Spain (Drs. Gómez, Sacristán, and Hernández); Eli Lilly and Company, Indianapolis, Ind. (Dr. Breier); and Centro Salud Mental Utrera, Seville (Dr. Carrasco); Hospital Universitario Son Dureta, Palma de Mallorca (Dr. Saiz); and Centro Salud Mental Collblanc, Barcelona (Dr. Carbonell), Spain.

Funded by Eli Lilly and Company.

Presented at the 11th annual meeting of the World Psychiatric Association, Aug 6–11, 1999, Hamburg, Germany; and the 12th annual meeting of the European College of Neuropsychopharmacology, Sept 21–25, 1999, London, England.

A complete list of the members of the EFESO Study Group appears at the end of this article.

Thanks are due to Raul Vara and Fernando Gonzalo, Biometrics Department, Phoenix International, Madrid, Spain.

Reprint requests to: Juan Carlos Gómez, Clinical Research Physician, Eli Lilly and Company, Avenida de la Industria 30, 28108 Alcobendas, Madrid, Spain (e-mail: gomez_juan-carlos@lilly.com).

The introduction of antipsychotic drugs during the 1950s represented a great step forward in the treatment of schizophrenia and other psychoses. The limitations of these drugs, in terms of both effectiveness and adverse effect profile, have, however, become evident over time. A high percentage of schizophrenic patients have an insufficient response to treatment with conventional antipsychotic medication, and up to 60% relapse 1 year after therapy.[2] Moreover, the high incidence of side effects associated with conventional antipsychotic drugs, particularly extrapyramidal symptoms (EPS), has greatly contributed to high relapse rates and poor compliance among patients.[3] All of these factors contribute to repeated hospital admissions and to progressive social and occupational dysfunction. These therapeutic limitations have made the availability of more effective and better tolerated drugs essential.

Until a few years ago, clozapine was the only drug that had demonstrated an improved therapeutic profile over that of the conventional antipsychotic drugs in terms of its effectiveness on resistant schizophrenic patients and the low incidence of extrapyramidal symptoms.[4] Nevertheless, the use of clozapine in practice has been limited owing to the risk of inducing agranulocytosis.

Olanzapine, a thienobenzodiazepine, is an antipsychotic drug with high in vitro affinity for the serotonergic receptors 5-HT_2 and 5-HT_6 and a somewhat lower affinity for 5-HT_3, as well as high in vitro affinity for dopaminergic receptors, mainly D_2, D_3, and D_4. It is also associated with high in vitro affinity for muscarinic $M_{1–5}$, α_1-adrenergic, and histaminergic H_1 receptors.[5,6] Electrophysiologic studies in animals suggest that olanzapine has a selective effect on the mesolimbic dopaminergic pathway originating in the A10 region, as opposed to the nigrostriatal A9 pathway.[7]

The safety and effectiveness of olanzapine have been studied in various placebo-controlled clinical trials,[8,9] as well as in trials controlled with haloperidol[10] and risperidone.[11] There were no treatment-emergent adverse events that occurred statistically significantly more frequently with olanzapine-treated patients compared with placebo-treated patients.[9] Treatment-emergent adverse events that occurred statistically significantly more frequently with olanzapine compared with haloperidol were excessive appetite and dryness of mouth.[10] In comparison with haloperidol and risperidone, olanzapine has been temporally associated with a lower incidence of extrapyramidal symptoms.[10,11]

The results of the clinical trials should be confirmed by means of effectiveness studies in daily clinical practice. This is particularly important in disorders such as schizophrenia in which the experimental situation of a clinical trial is often substantially different from daily clinical practice.[12] The experimental nature of a clinical trial makes it difficult for schizophrenic patients with a limited awareness of their illness to be included. Similarly, most clinical trials with antipsychotic drugs exclude patients with concomitant organic or psychiatric disorders, particularly disorders relating to substance abuse/dependence,[12] highly prevalent conditions in the population with schizophrenia.[13] In the same way, the limitations on the concomitant use of other antipsychotic drugs and the greater degree of control required to ensure compliance with treatment in most clinical trials are other factors that contribute to this distance between the experimental situation and daily clinical practice.

The benefits provided by the use of new antipsychotic drugs for the treatment of schizophrenia should be evaluated within the context of daily clinical practice in the patients receiving these drugs under the conditions in which they are used. This is where the observational epidemiologic surveys may play an important role. Nevertheless, observational studies are subject to obvious limitations, mainly caused by their nonrandomized nature, which should also be taken into account.

Currently, there is a paucity of data on the new antipsychotic drugs from pharmacoepidemiologic studies with control groups. The present article shows the results of the EFESO study (Estudio Farmacoepidemiologico en Esquizofrenia con Olanzapina [Pharmacoepidemiologic Study of Olanzapine in Schizophrenia]), the largest pharmacoepidemiologic study so far carried out with olanzapine, including a control group treated with other antipsychotic medication. The main objective of the study was the assessment of olanzapine's safety and particularly the presence of extrapyramidal symptoms in a cohort of patients treated under normal usage conditions, when compared with another cohort treated with other standard drugs.

METHOD

EFESO is an observation-based phase 4 prospective pharmacoepidemiologic study with an open comparison in parallel groups to assess the safety of olanzapine when compared with other antipsychotic drugs in the treatment of outpatients with schizophrenia. The study was designed with the aim of confirming the differences in the incidence of extrapyramidal symptoms between the olanzapine group and the control group, with a 90% power and a 2-tailed α risk of .05, to which end a sample size of approximately 1000 patients was estimated for each group. In addition, the olanzapine group contained twice the number of patients as the control group in order to detect, with an 80% power and an α risk of .05, any adverse effects occurring with a frequency of 1:1000 in the olanzapine group. In short, to meet its objectives, the study was designed to gather information on approximately 2000 patients treated with olanzapine and 1000 patients treated with other antipsychotic drugs.

The data were collected by a total of 293 psychiatrists, mostly in mental health centers or outpatient treatment units. Each participating psychiatrist collected data on those patients who were started on olanzapine therapy or on therapy with any other antipsychotic drug except clozapine during the inclusion period (October 1997 to February 1998) and who accepted inclusion in the study. Treatment indication was by means of purely clinical criteria, with no restrictions on the clinical handling of patients, and patients were not subject to any experimental intervention. No specific safety examination was mandatory in the protocol (electrocardiogram, hemogram, biochemical analysis, blood pressure, height, weight, etc.), as none of these tests are systematically carried out in patients with schizophrenia. The participating psychiatrists carried out these examinations whenever they considered them necessary and reported their results as adverse events whenever relevant. Data were collected over 3 visits: a baseline visit before starting the new treatment, after 3 months of treatment, and after 6 months of treatment. Patients discontinued the study when the principal antipsychotic prescribed at baseline was discontinued or for adverse events, lack of efficacy, or any other reason. Patients or physicians could stop their participation in the study at any point.

The study was carried out in accordance with Spanish legislation on pharmacologic monitoring and was authorized by the National Pharmacologic Monitoring Department. In line with these regulations, nonexperimental observational studies need not be approved by the ethics committees of the participating centers and the written consent of patients is not required. Researchers informed patients of the study's goals and obtained their verbal consent before collecting data. None of the study documentation contained details of the patients' identification. Only patients diagnosed as having schizophrenia (F.20 of ICD-10, World Health Organization[14]) were included when a change of medication was indicated or a new antipsychotic drug treatment was being initiated for whatever reason (insufficient response, persistence of positive symptoms, persistence of negative symptoms, poor tolerance, noncompliance, etc.).

The only patients excluded were those in whom antipsychotic drug therapy was contraindicated, those in whom clozapine therapy was indicated (restricted in Spain to patients with resistant schizophrenia), and those participating in clinical trials.

To limit selection bias, investigators were instructed to include all patients who received a new prescription of olanzapine or any other antipsychotic drug, who met inclusion/exclusion criteria, and who agreed to participate in the study until completing a block of 6 patients treated with olanzapine and 3 patients treated with other antipsychotics. Once a block was completed, investigators could include additional blocks until completion of the total sample. Selection of treatment was the investigators' choice; therefore, bias in treatment assignment could not be controlled.

To assess the main goal, all adverse events spontaneously reported by patients or identified in the course of the doctor-patient interview were recorded. Extrapyramidal symptoms were also noted by means of a short questionnaire, based on the extrapyramidal symptoms section of the UKU Side Effect Rating Scale,[15] dystonia, rigidity, hypokinesia, tremor, dyskinesia, and akathisia. Presence or absence of EPS was determined by individual investigators according to their own clinical criteria. All adverse events were coded using the Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART[16]) glossary.

Data were also collected on the overall clinical status of the patients by means of the Clinical Global Impressions-Severity (CGI-S) scale[17] and the Global Assessment of Function (GAF) scale,[18] which are generally regarded as standard instruments for clinical evaluation of patients with schizophrenia. Response to treatment was defined as a decrease of at least 2 points in the CGI-S score plus an endpoint CGI-S score of 4 or less. The study was monitored by Phoenix International–Madrid, Spain.

A total of 2967 schizophrenic patients were included in the study. Eighteen were excluded from the analysis because of inadequate baseline information. All the other patients have been taken into consideration for the statistical analysis, including those for whom data had been collected without strict application of the inclusion criteria (6 patients treated with clozapine and 1 patient treated with lorazepam), in accordance with the intention-to-treat principle.

Statistical Analysis

The statistical analysis was carried out by the biometrics department of Phoenix International. The data were keyed into 2 simultaneous databases by different individuals and later contrasted to eliminate errors. The system used for the verification, validation, and analysis of the data was SAS version 6.12 for Windows (SAS Institute, Cary, N.C.). Principal analyses compared the group treated with olanzapine versus the control group (those treated with other antipsychotics), because the main objective of the study was to compare olanzapine to standard treatment with any other drug. All patients who received olanzapine were included in the olanzapine group, and patients who did not were included in the control group. Nevertheless, to acknowledge for differences between different drugs in the control group, we decided a priori to conduct secondary analyses comparing the incidence of adverse events in the olanzapine group versus treatment-specific subgroups greater than N = 100.

The incidence of each adverse event in each group was calculated for the number of patients presenting the event at any time during the study over the total number of patients in the group. To analyze the changes in the clinical scales, we conducted an observed-case analysis for each visit, including the patients who had a baseline assessment and an assessment in the corresponding visit, as well as a last-observation-carried-forward (LOCF) analysis, including those patients with the baseline assessment and at least 1 postbaseline assessment. Quantitative variables were described using means, medians, standard deviations, and ranges. Discrete variables were described by means of frequency and percentage. For the statistical analysis of continuous variables, parametric and nonparametric tests were used depending on applicability constraints (normality and homoscedasticity) and the nature of the variable. For comparisons of age and number of years since the onset of the illness, single-factor analysis of variance (ANOVA) was used. Mean change in the CGI and GAF scales was analyzed by means of an ANOVA test. The number of adverse events and the number of extrapyramidal symptoms were compared using the Wilcoxon test. To analyze discrete variables (sex, type of schizophrenia, incidence of adverse events, percentage of patients responding, withdrawals caused by adverse events, and presence of concomitant treatments), the chi-square test or Fisher exact test was used. We considered a 2-tailed significance level of .05 for all tests.

Table 1. Drugs Prescribed as Principal Antipsychotic Treatment for Patients Included in the Study

Drug	N	%
Olanzapine	2128	72.2
Risperidone	417	14.1
Haloperidol	112	3.8
Sertindole	84	2.8
Zuclopenthixol	74	2.5
Fluphenazine	33	1.1
Trifluoperazine	31	1.1
Thioridazine	19	0.6
Perphenazine	18	0.6
Pimozide	11	0.4
Clozapine	6	0.2
Pipotiazine	4	0.1
Sulpiride	4	0.1
Chlorpromazine	3	0.1
Levomepromazine	3	0.1
Clotiapine	1	0.0
Lorazepam	1	0.0

Table 2. Demographic and Clinical Characteristics of the Sample at Baseline

Characteristic	Olanzapine (N = 2128)	Control Group (N = 821)	Statistic	p Value
Age (y)				
Mean (SD)	35.55 (11.68)	35.15 (11.25)	$F = 0.720$[a]	.4
Median	34	34		
Range	14–91	14–82		
Gender (% male)	63.7	63.6	$\chi^2 = 0.002$	.97
Time from onset (y)				
Mean (SD)	11.1 (9.55)	10.81 (9.3)	$F = 0.545$[a]	.46
Median	9	9		
Schizophrenia subtype (%)			$\chi^2 = 3.864$	.425[b]
Paranoid	64.7	65.9		
Undifferentiated	13.6	13.5		
Residual	12.8	10.6		
Disorganized	8.4	9.2		
Catatonic	0.5	0.9		
Baseline CGI-S score				
Mean (SD)	4.66 (0.9)	4.63 (0.9)	$Z = -1.0115$[c]	.312
Baseline GAF score				
Mean (SD)	44.9 (14.77)	45.1 (15.24)	$F = 0.190$[a]	.663

[a]Analysis of variance.
[b]Overall p value.
[c]Wilcoxon test.

RESULTS

Table 1 shows the list of drugs that were prescribed as principal treatment in the study. Despite the nonrandomized nature of the study, there were no statistically significant differences between the 2 groups in any of the baseline demographic or clinical characteristics (Table 2).

Table 3 gives the mean and the median dose used throughout the study for olanzapine and the 2 drugs most frequently used in the control group (haloperidol and risperidone). The initial dose is the prescribed dose at baseline, whereas the mean dose is calculated from the mean dose received by each patient during the study. A higher percentage of patients in the control group received some kind of concomitant treatment in comparison with the olanzapine group (control 57.9% vs. olanzapine 36.3%, $\chi^2 = 99.026$, $p < .001$, at 6 months). Specifically, a lower percentage of the patients in the olanzapine group received anticholinergic medication when compared with the control group or with the haloperidol and risperidone subgroups (at 6 months, olanzapine 10.2% vs. control group 26.8%, $\chi^2 = 109.188$, $p < .001$; vs. risperidone 19.9%, $\chi^2 = 28.105$, $p < .001$; and vs. haloperidol 44%, $\chi^2 = 103.001$, $p < .001$).

Table 3. Initial and Mean Dose of Olanzapine and Other Antipsychotic Drugs in the Study

Dose	Olanzapine (N = 2122)	Risperidone (N = 414)	Haloperidol (N = 108)
Initial dose[a]			
Mean (SD)	12.23 (4.85)	5.18 (2.32)	13.92 (9.26)
Median	10	6	10
Range	5–30	1.5–30	2–50
Mean dose[b]			
Mean (SD)	13.01 (4.97)	5.39 (2.5)	13.64 (8.72)
Median	10	6	10
Range	5–30	1.5–30	2–40

[a]Dose prescribed at baseline.
[b]Calculated from the mean dose received by each patient during the study.

Table 4. Reason for Discontinuation From the Study by Treatment Group

Status	Olanzapine (N = 2128) N	Olanzapine (N = 2128) %	Control Group (N = 821) N	Control Group (N = 821) %	Statistic
Protocol completed	1564	73.5	627	76.4	
Adverse event	40	1.9	18	2.2	
Patient decision	29	1.4	8	1.0	
Lack of efficacy	31	1.5	9	1.1	
Death	3	0.1	1	0.1	
Lost to follow-up[a]	381	17.9	125	15.2	$\chi^2 = 4.832$
Other	80	3.8	33	4.0	$p = .566$[b]

[a]The category "lost to follow-up" includes those patients who did not have a final evaluation available.
[b]Overall p value.

Table 4 indicates the dropout rate distributed by the various possible causes. There were 3 patients who died in the olanzapine group: 1 suicide, 1 patient with acquired immunodeficiency syndrome, and 1 87-year-old patient who died for reasons unrelated to the antipsychotic treatment. In the control group, 1 patient committed suicide. There were no significant differences in the reasons for withdrawal between the 2 groups.

A higher percentage of the patients in the control group (64%) had at least 1 adverse event at some time in the study, a statistically significant difference ($p < .001$) when compared with the olanzapine group (48%). Similarly, a higher percentage suffered some kind of extrapyramidal symptom in the control group (57%), collected through the questionnaire, in comparison with the olanzapine group (37%), and this difference was also significant ($p < .001$). The percentage of patients with an adverse

Table 5. Treatment-Emergent Adverse Events That Were Reported With a Significantly Different Rate in the Olanzapine Group Compared With Risperidone and Haloperidol Subgroups, Classified and Coded According to the COSTART[a] Dictionary

	Olanzapine (N = 2128)		Risperidone (N = 417)		Olanzapine vs Risperidone		Haloperidol (N = 112)		Olanzapine vs Haloperidol	
Event	N	%	N	%	χ^2	p	N	%	χ^2	p
All patients										
Akathisia	59	2.8	30	7.2	20.200	.001	19	17.0	63.761	.001
Dystonia	24	1.1	9	2.2			4	3.6	5.147	.048
Extrapyramidal syndrome	6	0.3	3	0.7			4	3.6	25.905	.001
Hypertonia	73	3.4	35	8.4	21.134	.001	29	25.9	123.521	.001
Hypokinesia	104	4.9	36	8.6	9.412	.002	30	26.8	90.720	.001
Hypotension	4	0.2	1	0.2			2	1.8	10.168	.033
Somnolence	96	4.5	7	1.7	7.204	.007	5	4.5		
Tremor	140	6.6	47	11.3	11.275	.001	29	25.9	56.900	.001
Weight gain	146	6.9	8	1.9	14.982	.001	1	0.9	6.180	.013
Men	(N = 1349)		(N = 274)				(N = 68)			
Abnormal ejaculation	0		2	0.73	9.859	.028	0			
Impotence	0		2	0.73	9.859	.028	0			
Women	(N = 769)		(N = 142)				(N = 44)			
Amenorrhea	5	0.65	5	3.52	9.100	.011	0			

[a]COSTART= Coding Symbols for Thesaurus of Adverse Reaction Terms.[16]

event or an extrapyramidal symptom in the course of the study was lower in the olanzapine group when compared with the subgroups treated with haloperidol and risperidone ($p \leq .001$ in all cases).

Adverse events that were reported with statistically significantly greater incidence in the olanzapine group compared with the control group were somnolence and weight gain, whereas reported akathisia, dystonia, extrapyramidal syndrome, hypertonia, hypokinesia, and tremor were significantly more frequent in the control group compared with the olanzapine group. Abnormal ejaculation and impotence were also reported significantly more frequently among men in the control group. Table 5 presents those adverse events that appeared with a statistically significantly different incidence rate in the olanzapine group compared with the patients treated with risperidone or haloperidol.

The greater incidence rate of various extrapyramidal symptoms is worth highlighting in the control group, despite the higher use of anticholinergic medication in the control group. There were no differences in the incidence rate of anticholinergic-type symptoms (dry mouth, constipation, diplopia, urinary retention, difficulties in concentration, and confusion). There were 2 cases of mild leukopenia in the olanzapine group, not associated with clinical symptoms. One of these was a transient case of mild leukopenia, which returned to normal levels during treatment with olanzapine. The second case was also mild (total leukocytes = 3500/mm^3), basically due to a reduction in lymphocytes. The patient had previously been diagnosed for lymphopenia. There were no cases of agranulocytosis in the study.

The adverse events reported in the olanzapine group did not include any clinically relevant problems potentially associated with the treatment.

Table 6 gives the mean change in the CGI-S and GAF scores. There was some improvement in both treatment groups (reduction of the mean score in the CGI-S and an increase in the GAF), although the improvement was significantly greater in the olanzapine group. Response rate at 6-month follow-up was also significantly greater in the olanzapine group. The percentage of patients with an improvement of at least 1 point on the CGI-S scale at the 6-month follow-up was significantly greater in the olanzapine group than in the control group (73.5% and 64%, respectively; p = .001). A small percentage of similar size in both groups had a slight worsening of the global clinical impression (2.9% and 2.8%, respectively; NS).

DISCUSSION

The EFESO study is the largest prospective observational study conducted with atypical antipsychotics of which we are aware. Nevertheless, it reflects the difficulties and limitations inherent in large observational studies: (1) selection bias secondary to lack of randomization; (2) additional problems in establishing unequivocal causal relationship, due to a heterogenous control group and frequent use of concomitant medication; (3) difficulty in keeping strict control of the study due to the size of the study and the number of participants, as shown by the inclusion of a few patients who did not meet study criteria and lack of complete information; (4) majority of dropouts due to unknown reasons; and (5) probable underreporting of adverse events compared with clinical trials. Acknowledging these limitations, we report the overall results of the study, including all patients to give an unbiased picture of what happened in the study and to be consistent with the primary objective, which was to evaluate the safety of olanzapine compared with other routine clinical treatments.

A secondary objective was to evaluate the effectiveness of olanzapine compared with other routine clinical treatments. The study has the advantage of including a control group, in contrast to other observational studies with antipsychotics published recently.[19,20] The number of patients included in this study is particularly noteworthy, since it makes this particular study the largest prospective observational analysis with antipsychotic drugs of which we are aware. The retention rate for our study has also been very high (approximately 75%) in comparison with controlled clinical trials. For instance, 57.6% of patients treated with olanzapine and 47.3% of patients treated with risperidone completed a 6-month follow-up in the study by Tran et al.[11] Most of the dropouts were due to lack of follow-up, with the true reason for patient withdrawal unknown, probably reflecting well the normal situation during treatment of patients with schizophrenia by clinical psychiatrists. More patients were included in the olanzapine group than had been planned (72% versus 67% of the total sample). This is probably due to the fact that olanzapine had been available on the Spanish market for less than a year when the study was carried out; therefore, there were more situations in which the replacement of previous treatments by olanzapine was indicated rather than the replacement of other antipsychotic drugs. A significantly greater percentage of patients were included in the olanzapine group than in the control group due to the lack of efficacy or intolerance of earlier treatments, whereas a larger percentage was included in the control group due to noncompliance or the start of antipsychotic therapy. There were 7 patients included by error, as 6 received treatment with clozapine and 1 with lorazepam without antipsychotic treatment. These patients have been included in the analysis.

In general, most patients started antipsychotic therapy because of ineffectiveness or poor tolerance of previous treatments. The percentage of patients entering the study in the olanzapine group for such reasons was, however, greater than in the control group, whereas the situation was reversed in the case of patients newly starting treatment. Despite this, the samples were very similar in both groups.

The mean dose of olanzapine is similar to the 13.2 mg/day mean dose in a controlled clinical trial where the dose could be flexibly varied between 5 and 20 mg/day.[10] The mean dose of risperidone is consistent with the doses used in the registration clinical trials, 6 mg/day[21,22] and 4 to 8 mg/day,[23] and somewhat lower than that used in another prospective naturalistic study, 6.1 mg/day in Canada.[19]

A large proportion of patients from both the olanzapine and control groups received concomitant treatment with antipsychotics, benzodiazepines, anticholinergics, or other drugs. Therefore, it is difficult to attribute unequivocally to olanzapine or to other specific drugs the safety and effectiveness results. Nevertheless, we estimate that the value of these data is that they reflect the routine clinical practice where antipsychotics are frequently used in combination.

Table 6. Mean Change in the Clinical Global Impressions-Severity (CGI-S) and Global Assessment of Functioning (GAF) Scales at Endpoint by Treatment Group (last observation carried forward) and Treatment Response at 6-Month Follow-Up

Measure	Olanzapine	Control Group	Statistic	p Value	Difference Olanzapine-Control Group
CGI-S					
N	1998	768	ANOVA		
Decrease, mean (SD)	1.19 (1.15)	1.02 (1.12)	F = 11.84	< .001	D = 0.17
95% CI	1.14 to 1.24	0.94 to 1.1			0.076 to 0.264
GAF					
N	1983	766	ANOVA		
Increase, mean (SD)	18.34 (18.18)	16.13 (16.44)	F = 8.56	.004	D = 2.21
95% CI	17.5 to 19.1	15.0 to 17.3			0.737 to 3.683
Response rate at 6 months[a]					
N	1794	706			
Number of responders	669	211	$\chi^2 = 12.24$	< .001	D = 7.4%
%	37.3	29.9			3.3% to 11.4%[b]

[a]Response to treatment was defined a priori as a decrease in the CGI-S score of at least 2 points, plus an endpoint CGI-S of 4 points or less.
[b]95% CI.

Adverse Events

The low incidence of patient withdrawals due to adverse events in the course of this study is noteworthy, although it is probably true that some of the patients who were lost to follow-up discontinued because of adverse events. The safety profile collected from the patients treated with olanzapine is consistent with the profile shown in the registration clinical trials and included in the product's package insert. There have been no unexpected safety problems of clinical relevance.

The only adverse events included in the European Summary of Product Characteristics (SPC) with a frequency exceeding 10% of that recorded in the registration trials with olanzapine were somnolence and weight gain (Zyprexa, European SPC), and these same adverse events were the only ones noted in the present study with a significantly greater incidence than in the control group. The absolute level of incidence is lower than that recorded in the registration trials (somnolence 4.5% and weight gain 6.9%). This difference could be related to the closer follow-up to which patients are subjected in clinical trials, but we feel, however, that the incidence in the present study may more closely approximate the incidence of clinically significant cases of both events. It is of interest

that the incidence of somnolence in the olanzapine group was the same as in the subgroup of patients treated with haloperidol.

The present study is noteworthy for the lack of any reports of agranulocytosis in the olanzapine group. The incidence of alterations in hepatic enzymes with olanzapine could not be evaluated in this study because there was no systematic determination in all patients. Nonetheless, there have been no cases of jaundice or clinical hepatic disease in connection with olanzapine in this study. Alterations in hepatic function tests are frequent with conventional antipsychotic drugs according to the literature,[24] but there have been no reported cases in the present study. The incidence of seizures with olanzapine was 0.1% and not significantly different from the control group in this study. The reported incidence of seizures in the literature with conventional antipsychotic drugs is less than 1%, whereas it is approximately 5% with clozapine and is dose-dependent.[24]

The incidence of extrapyramidal symptoms was low in the olanzapine group, and if we take into account that the concomitant use of other antipsychotic drugs was allowed, we might think that the incidence with olanzapine monotherapy would have been even lower. This low incidence confirms the results of controlled clinical trials in which olanzapine has been shown to have a lower incidence of extrapyramidal symptoms in comparison with haloperidol[10] and risperidone.[11] The present study confirms this lower incidence of extrapyramidal symptoms in routine clinical practice as well as the lower level of anticholinergic use in olanzapine-treated patients. In the comparison of EPS incidence, it is important to take into account the comparability of the dosage administered. In the present study, patients received the doses that their doctors considered to be optimal in terms of the efficacy/tolerability ratio. In 2 observational studies with risperidone in 439 patients[20] and in 330 patients,[19] the incidence of EPS is not reported; rather, they merely report the mean changes in the EPS assessment scales, thus making it difficult to draw comparisons with our study. In the article by Tran et al.,[11] the incidence of reported EPS is calculated in a clinical trial. The incidence of an extrapyramidal symptom was significantly greater with risperidone than with olanzapine (31.1% versus 18.6%), as was the incidence of dystonia (6% versus 1.7%) and parkinsonism (18.6% versus 9.9%). The incidence of EPS in our study is less than that reported by Tran et al.[11] This may be attributable to the differences between a clinical trial with frequent visits, where any appearance of EPS can probably be detected, and those arising in an observational study with assessments more spread out. On the other hand, it must be remembered that the mean doses used for both risperidone and olanzapine were greater in the study by Tran et al.[11]

The incidence of anticholinergic effects (dry mouth, constipation, diplopia, urinary retention, difficulties in concentration, and confusion) was lower than 1% in all groups, and there were no significant differences between the patients treated in the olanzapine group and the control group or the subgroups treated with risperidone and haloperidol. This confirms that olanzapine, despite having a high in vitro affinity with muscarinic receptors, presents in vivo a slight/moderate anticholinergic activity.[6]

Summary

The improvement shown by the olanzapine group on the CGI-S and GAF scores, along with the treatment-retention rate, confirms the effectiveness of olanzapine in the treatment of schizophrenia in clinical practice. Nevertheless, it is risky to draw conclusions on the differences in clinical improvement (CGI-S and GAF) between the olanzapine group and the control group, since the present study was not designed for the evaluation of efficacy. Although the olanzapine group and the control group were not significantly different at baseline in the variables analyzed, we may not rule out that the groups were different in other relevant variables which we have not checked. There may also have been differences in how patients were assessed or treated throughout the study, given the unblinded nature of the study. However, the results are consistent with the results from a controlled clinical trial that included flexible dosing of olanzapine and haloperidol.[10]

There is an interesting question as to whether the small yet significant differences in clinical improvement in favor of olanzapine might be due to the contribution of the negative symptoms on the CGI-S and GAF scores. It is also necessary to take into account the impact of EPS: a high percentage of patients treated with antipsychotic drugs suffer from dysphoria (related to extrapyramidal symptoms), particularly akathisia.[25] The lower incidence of akathisia with olanzapine in comparison with haloperidol and risperidone may have contributed to the differences in the global clinical assessment detected in the present study. The potential overlap between negative symptoms of schizophrenia and hypokinesia may have also contributed to the slightly better global outcome in the olanzapine group. In summary, the greater overall clinical improvement in the olanzapine group compared with the control group may reflect a real, though small, difference in effectiveness or the consequences of different EPS rates or a confounding factor not well controlled in an observational study.

In conclusion, the present study confirms that olanzapine is an effective and well-tolerated treatment in an unselected population of patients with schizophrenia. The safety profile is consistent with the product's data sheet.

Drug names: chlorpromazine (Thorazine and others), clozapine (Clozaril and others), haloperidol (Haldol and others), lorazepam (Ativan and others), olanzapine (Zyprexa), perphenazine (Trilafon and others), pimozide (Orap), risperidone (Risperdal), thioridazine (Mellaril and others), trifluoperazine (Stelazine).

REFERENCES

1. Brenner HD, Dencker SJ, Goldstein MJ, et al. Defining treatment-refractoriness in schizophrenia. Schizophr Bull 1990;16:551–561
2. Kane JM. Schizophrenia. N Engl J Med 1996;334:34–41
3. Weiden PJ, Shaw E, Mann JJ. Causes of neuroleptic noncompliance. Psychiatr Ann 1986;16:571–575
4. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic: a double blind comparison with chlorpromazine. Arch Gen Psychiatry 1988;45:789–796
5. Bymaster FP, Calligaro DO, Falcone JF, et al. Radioreceptor binding profile of the atypical antipsychotic olanzapine. Neuropsychopharmacology 1996;14:87–96
6. Bymaster F, Perry KW, Nelson DL, et al. Olanzapine: a basic science update. Br J Psychiatry 1999;174(suppl 37):36–40
7. Stockton ME, Rasmussen K. Electrophysiological effects of olanzapine, a novel atypical antipsychotic, on A9 and A10 dopamine neurons. Neuropsychopharmacology 1996;14:97–104
8. Beasley CM Jr, Tollefson GD, Tran P, et al. Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 1996;14:105–118
9. Beasley CM, Sanger T, Satterlee W, et al. Olanzapine versus placebo: results of a double-blind, fixed-dose olanzapine trial. Psychopharmacology 1996;124:159–167
10. Tollefson GD, Beasley CM Jr, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia, schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997;154:157–165
11. Tran PV, Hamilton SH, Kuntz AJ, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997;17:407–418
12. Collaborative Working Group on Clinical Trial Evaluations. Clinical development of atypical antipsychotics: research design and evaluation. J Clin Psychiatry 1998;59(suppl 12):10–16
13. Buckley PF. Substance abuse in schizophrenia: a review. J Clin Psychiatry 1998;59(suppl 3):26–30
14. World Health Organization. International Classification of Diseases. Mental and Behavioural Disorders, 10th ed. Geneva, Switzerland: World Health Organization; 1994
15. Lingjaerde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale: a new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl 1987;334:1–100
16. COSTART. Coding Symbols for Thesaurus of Adverse Reaction Terms. Rockville, Md: US Department of Health and Human Services; 1990
17. National Institute of Mental Health. Clinical Global Impressions. In: Guy E, ed. ECDEU Assessment for Psychopharmacology, Rev. Rockville, Md: National Institute of Mental Health; 1976
18. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Press; 1994
19. Chouinard G, Kopala L, Labelle A, et al. Phase IV multicentre clinical study of risperidone in the treatment of outpatients with schizophrenia. Can J Psychiatry 1998;43:1018–1025
20. Gutierrez M, Gibert J, Bobes J, et al. Risperidona en el tratamiento de la reagudización de los síntomas de la esquizofrenia. Actas Luso-Esp Neurol Psiquiatr 1998;26:83–89
21. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed-doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol 1993;13:25–40
22. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825–835
23. Peuskens J and the Risperidone Study Group. Risperidone in the treatment of patients with chronic schizophrenia: a multinational, multi-centre, double-blind, parallel group study versus haloperidol. Br J Psychiatry 1995;166:712–726
24. Simpson GM, Pi EH, Sramek JJ. Neuroleptics and antipsychotics. In: Dukes MNG, ed. Meyler's Side Effects of Drugs. Amsterdam, the Netherlands: Elsevier; 1996
25. Van Putten T, May PR, Marder SR, et al. Subjective response to antipsychotic drugs. Arch Gen Psychiatry 1981;38:187–190

Acknowledgment: Participants in the EFESO Study Group

Patricio Ruiz, M.D.; César Antón, M.D.; Eva Fontova, M.D.; Eduardo Ortega, M.D.; Alfonso Santiso, M.D.; Iñaki Márquez, M.D.; Óscar Taboada, M.D.; Fernando García, M.D.; José Montero, M.D.; Ernesto Capdevila, M.D.; Cristina Hernández, M.D.; Salvador Gimeno, M.D.; Raúl Fernández, M.D.; Antonio Arumi, M.D.; José Ignacio Mendezona, M.D.; Emilio González, M.D.; Enrique Aragués, M.D.; Montserrat García, M.D.; Carlos Carmona, M.D.; Juan Luis Figuerido, M.D.; José Luis Rodríguez, M.D.; Juan Ramón Sambola, M.D.; Fernando Teba, M.D.; Felisa Gómez, M.D.; Elena Lozano, M.D.; Jehad Kamel Suleiman, M.D.; Antonio Agüera, M.D.; Javier Aztarain, M.D.; Carmelo Pelegrín, M.D.; Eduard Vieta, M.D.; Marisa Terradillos, M.D.; Adriana Salesansky, M.D.; Lidia Cuesta, M.D.; María Echeveste, M.D.; Blas Erquicia, M.D.; Justo José Cano, M.D.; Antonio Micol, M.D.; José Antonio Muñoz, M.D.; Delio Guerro, M.D.; Francisco Pérez, M.D.; Juan Carlos Ortigosa, M.D.; Ramón Mira, M.D.; José Lonjedo, M.D.; Joaquín Sama, M.D.; Norma Silveira, M.D.; Rodrigo Cabrera, M.D.; Carles Argila, M.D.; Asunción Pascual, M.D.; Ildefonso Gómez Feria, M.D.; Pastora Cuevas, M.D.; Cristina Del Álamo, M.D.; Jesús J. Padin, M.D.; José Antonio Soto, M.D.; Ángel Royuela, M.D.; Enrique Pérez, M.D.; José María Monjil, M.D.; Sergio Ocio, M.D.; Leopoldo Elvira, M.D.; Juan Félix Perianes, M.D.; José María Giralt, M.D.; José Vicente Baeza, M.D.; Ángel Luis Montejo, M.D.; Pedro Megía, M.D.; Milagros Escobar, M.D.; Santiago Sánchez, M.D.; Remei Albert, M.D.; Pablo Malo, M.D.; Blas Bombín, M.D.; Luis Pacheco, M.D.; Fidel Monjas, M.D.; Juan Gil, M.D.; Manuel Celma, M.D.; Adolfo Revuelta, M.D.; Jesús González, M.D.; Germán Molina, M.D.; José Santiago Doncel, M.D.; Pilar Lusilla, M.D.; Aurelio García, M.D.; Aina Alzamora, M.D.; Sergio Oliveros, M.D.; Francisco Javier Samino, M.D.; Montserrat Verdera, M.D.; José Ramón López, M.D.; Inmaculada Mosqueira, M.D.; María Victoria Olles, M.D.; José Ramón Domenech, M.D.; Néstor Szerman, M.D.; José María Blázquez, M.D.; Juan Carlos Berenguer, M.D.; Ana Mencía, M.D.; Adolf Mas-Yebra, M.D.; Visitación Palomero, M.D.; Manuel Franco, M.D.; Joan María Ferrer, M.D.; Javier Blanco, M.D.; Pepe Romeu, M.D.; Isabel Lozano, M.D.; Esperanza Almenta, M.D.; José Gascón, M.D.; Diego Jimenez, M.D.; Antonio Corominas, M.D.; Jorge Grijalbo, M.D.; Sergio González, M.D.; Antonio Delgado, M.D.; Francisco de Paula Albert, M.D.; Javier Ortiz, M.D.; Concepción Sanz, M.D.; José Matarredona, M.D.; José María Correas, M.D.; Pedro Malabia, M.D.; Belén Díaz, M.D.; Jordi Pujol, M.D.; Júlia Fraga, M.D.; Antonio Carrillo, M.D.; José Antonio García, M.D.; Ricard Reixach, M.D.; Diego Pulido, M.D.; Antonio Francisco Aba, M.D.; Tirso Ventura, M.D.; Emilia Ferrandiz, M.D.; Álvaro Irvin, M.D.; Diego Arenas, M.D.; Ángel Luis Blanco, M.D.; Paz Puchades, M.D.; Ramón Palmer, M.D.; Santiago López, M.D.; Isabel Irigoyen, M.D.; Carles Martínez, M.D.; Esther Carrasco, M.D.; Néstor Mártinez, M.D.; José Alfredo Pérez, M.D.; Juan Ignacio Franch, M.D.; Antonio Alfonso Soto, M.D.; Félix Martín, M.D.; María José Gómez, M.D.; Francisca Almansa, M.D.; María Jesús Merino, M.D.; María Inmaculada Ortíz-Cañavate, M.D.; Álvaro Rivera, M.D.; Enrique Sánchez, M.D.; Juan José López,

M.D.; Manuel Camacho, M.D.; Juan Carlos Díaz, M.D.; Fernando Navarro, M.D.; Esperanza De Miguel, M.D.; Francisco Arias, M.D.; Elisa Valero, M.D.; Juan Francisco Bort, M.D.; Carmen Busuldo, M.D.; Miguel Ángel Ortega, M.D.; Auxiliadora Romero, M.D.; María José Alastruey, M.D.; Jordi Pujiula, M.D.; José Javier Martínez De Morentín, M.D.; Juan Mons, M.D; Esperanza Álvarez-Estrada, M.D; Juan Gea, M.D.; Ángel Segura, M.D.; Luis Gutierrez, M.D.; Ramona Lucas, M.D.; Alfredo Galindo, M.D.; Araceli Sánchez, M.D.; Jesús Fernández, M.D; Fernando Megías, M.D.; José Escudero, M.D.; Luis Agüera, M.D.; María Ángeles Saínz, M.D.; Ángela Navarro, M.D; José Ildefonso Pérez, M.D.; Juan Mendiví, M.D.; Nicolás Pérez, M.D.; Javier Ruiz, M.D; Manuel Alejandre, M.D; José Castro, M.D.; Micaela Más, M.D.; José De Santiago, M.D.; Jesús Monforte, M.D.; José Antonio López, M.D.; Juan Luis Vélez, M.D.; José Ignacio Portilla, M.D.; Cristina Moreno, M.D.; Milagros Sánchez, M.D.; José María Blanco, M.D.; María Ángeles Foz, M.D.; Bosco Anguiano, M.D.; Gustavo Faus, M.D.; José Salazar, M.D.; Luis Fernando Martín, M.D.; Vicente Elvira, M.D.; Lourdes Estévez, M.D.; María Teresa Lorenzo, M.D.; Cecilio Calzado, M.D.; Pascual Tabares, M.D.; Manuel Soria, M.D.; Luis Docasar, M.D.; Antonio Plaza, M.D; María José González, M.D.; Miguel Ángel Martínez, M.D.; José Luis Santos, M.D.; Alfredo García de Vinuesa, M.D.; Rosa Pérez, M.D.; Antonio Galbis, M.D.; Eulalio Valmisa, M.D.; Pedro Angona, M.D.; Alicia Díaz, M.D.; Pablo Quiroga, M.D.; Fernando Contreras, M.D.; Juan Pablo Saenz, M.D.; Juán Morcillo, M.D.; María Dolores Alonso, M.D.; Ramiro Bravo, M.D.; Manuel Conde, M.D.; Carmen Martín, M.D.; Róser Guillanat, M.D.; Carlos Ganoza, M.D.; Juan Cadevall, M.D.; Tomás Alcaina, M.D.; Emma Osejo, M.D.; Andrés Roig, M.D.; Miguel Bautista, M.D.; Ana Torcal, M.D.; Miguel Caballería, M.D.; Andrés Sandoval, M.D.; Julio Bobes, M.D.; María Jesús Luna, M.D.; Avelina Pérez, M.D.; Emilio Rodríguez, M.D.; Saturio Leal, M.D.; Rosa Cano, M.D.; Pilar Cano, M.D.; José Javier Morales, M.D.; Francisco Ferre, M.D.; Josefa Matías, M.D.; José Manuel Montes, M.D.; María Paz García, M.D.; Miguel Ángel Haza, M.D.; Diego Palao, M.D.; Dolores Azkunaga, M.D.; Antonio Rey, M.D.; Alberte Arauxo, M.D.; Xavier Cardona, M.D.; María Ángeles Medina, M.D.; Consuelo de Dios, M.D.; Joaquín López, M.D.; José María García, M.D.; Manuel Cumella, M.D.; Eduardo Balbo, M.D.; Manuel Arias, M.D.; Javier Rodríguez, M.D.; Dionisio Romero, M.D.; Gabriel Caffaro, M.D.; César Azpeleta, M.D.; Miguel Gelabert, M.D.; Eulalia Carrato, M.D.; Manuel Serrano, M.D.; Marina Puigdellivol, M.D.; Julio Quiles, M.D.; Miguel Verdeguer, M.D.; Iciar López, M.D.; Francisco Doce, M.D.; Joaquín López, M.D.; José Manuel Olivares, M.D.; Alberto Varona, M.D.; Susana Bescos, M.D.; Francisco José Otero, M.D.; José Vilar, M.D.; Cristina Anchustegui, M.D.; María Fé Bravo, M.D.; Guillermo Rendueles, M.D.; Antonio Luis Pérez, M.D.; Santiago Vega, M.D.; Demetrio Mármol, M.D.; Lorenzo Prado, M.D.; Ana Montes, M.D.; José Pérez, M.D.; Jesús Paulino Alonso, M.D.; Antonio González-Quirós, M.D.; Ignacio Sánchez, M.D.; Juan Antonio Romero, M.D.; Lluis Jordá, M.D.; Carlos Soler, M.D.; José Ignacio Aznarte, M.D.; Hugo Pachas, M.D.; Ramón Sancho, M.D.; Ángela Ibáñez, M.D.; Manuel Guillén, M.D.; María del Pino Morales, M.D.; Francisco Javier Alberca, M.D.; Ana González, M.D.; Ángel DeHaro, M.D.