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Progress in Neuro-Psychopharmacology & Biological Psychiatry 29 (2005) 944 – 951

Progress In Neuro-Psychopharmacology & Biological Psychiatry

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Safety and effectiveness of olanzapine in monotherapy: A multivariate analysis of a naturalistic study

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Accepted 18 April 2005
Available online 13 June 2005

Abstract

Background: This study investigated safety and effectiveness of olanzapine in monotherapy compared with conventional antipsychotics in treatment of acute inpatients with schizophrenia.
Method: This was a prospective, comparative, nonrandomized, open-label, multisite, observational study of Spanish inpatients with an acute episode of schizophrenia. Data included safety assessments with an extrapyramidal symptoms (EPS) questionnaire and the report of spontaneous adverse events, plus clinical assessments with the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impressions-Severity of Illness (CGI-S). A multivariate methodology was used to more adequately determine which factors can influence safety and effectiveness of olanzapine in monotherapy.
Results: 339 patients treated with olanzapine in monotherapy (OGm) and 385 patients treated with conventional antipsychotics (CG) were included in the analysis. Treatment-emergent EPS were significantly higher in the CG ($p < 0.0001$). Response rate was significantly higher in the OGm ($p = 0.005$). Logistic regression analyses revealed that the only variable significantly correlated with treatment-emergent EPS and clinical response was *treatment strategy*, with patients in OGm having 1.5 times the probability of obtaining a clinical response and patients in CG having 5 times the risk of developing EPS.
Conclusion: In this naturalistic study olanzapine in monotherapy was better-tolerated and at least as effective as conventional antipsychotics.

Keywords: Acute episode; Conventional antipsychotics; Inpatients; Naturalistic study; Olanzapine in monotherapy; Schizophrenia

1. Introduction

Schizophrenia is a major psychiatric disorder with an early age of onset, a chronic course, and a consequent adverse impact on patients' family, social, and occupational life. Positive symptoms of schizophrenia lead to an interruption in coherent thinking, anxiety, and difficulties performing daily activities. Negative symptoms have an adverse impact on social functioning leading to loneliness

Abbreviations: BPRS, Brief Psychiatric Rating Scale; CA, conventional antipsychotics; CG, group of patients treated with conventional antipsychotics; CGI-S, Clinical Global Impression of Severity; EPS, extrapyramidal symptoms; ICD-10, International Classification of Diseases: Mental and Behavioral Disorders, 10th edition; LOCF, Last Observation Carried Forward; NOSIE, Nurses' Observation Scale for Inpatient Evaluation; OGm, Group of patients treated with olanzapine in monotherapy; UKU, Udvalg for Kliniske Unders∅gelser (Lingjaerde Side Effect Rating Scale); WHO, World Health Organization.

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doi:10.1016/j.pnpbp.2005.04.037

and isolation (Breier, 2001). Affective symptoms, which are very common in patients with schizophrenia, are partially responsible for the high suicide rate reported among these patients and also for the decrease in their quality of life (Tollefson and Andersen, 1999). Finally, cognitive symptoms also affect patients' social and occupational life (Green, 1996). Despite the fact that the majority of patients recover from their first episode of schizophrenia (Tohen et al., 1992), they have a high risk of relapse and progressive deterioration (Hegarty et al., 1994; Szymanski et al., 1995).

Conventional antipsychotics permitted a majority of patients with schizophrenia to be treated in the community, dramatically reducing the time they spent in hospitals. These drugs have been used to treat acute psychotic episodes, allowing for prompt hospital discharge as well as for establishing the basis for long-term management of the disease. However, these conventional antipsychotics are subject to certain limitations for the optimal management of acute psychotic patients. Although these drugs are effective for treatment of positive symptoms, their effectiveness in treating negative, affective, and cognitive symptoms is generally very scarce or even non-existent. Moreover, the relapse rate among patients with schizophrenia treated with conventional antipsychotics goes up to 60% during the year following hospital admission (Kane, 1996). In addition, conventional antipsychotics cause many side effects, especially extrapyramidal symptoms (EPS) including parkinsonism, dystonia, akathisia, and tardive dyskinesia (Levinson et al., 1990) that, due to the discomfort they cause, contribute to repeated hospital admissions with the consequent risk of progressive clinical, cognitive, and social deterioration.

Bearing this in mind, the emergence of the new-generation atypical antipsychotics represented a ray of hope in the treatment of patients with schizophrenia, particularly because of their better tolerability and efficacy for treatment of negative and affective symptoms compared with conventional antipsychotics (Beasley et al., 1996; Collaborative Working Group on Clinical Trial Evaluation, 1998; Mortimer et al., 2003; Wheeler-Vega et al., 2003). Olanzapine, one of these atypical antipsychotics, has been demonstrated in several controlled clinical trials to have at least the same efficacy as conventional antipsychotics, and olanzapine-treated patients had a much lower rate of extrapyramidal adverse events (Beasley et al., 1996, 1997; Tollefson et al., 1997a,b).

However, the experimental conditions of clinical trials make it difficult to extrapolate their results to normal clinical practice, as patients with little understanding of their disease, co-morbid physical or psychiatric conditions, or concomitant use of other drugs are usually excluded from these studies. Thus, the efficacy results of clinical trials are complemented by naturalistic studies that reproduce daily clinical practice more precisely. However, these naturalistic studies also have several limitations, such as selection bias due to lack of randomization, probable underreporting of adverse events compared with clinical trials, and difficulties in establishing unequivocal causal relationships due to the frequent use of concomitant medication.

In this study, we have tried to minimize the last mentioned limitation of naturalistic studies assessing the safety, especially regarding EPS, and effectiveness of olanzapine when used in monotherapy compared with conventional antipsychotics in a cohort of patients with schizophrenia admitted to psychiatric units and otherwise treated under routine clinical conditions. A previous manuscript on the whole sample of patients which took part in the EUROPA study (Álvarez et al., 2003) reported a higher incidence of treatment-emergent EPS in the group of patients treated with olanzapine plus conventional antipsychotics compared with those treated with olanzapine in monotherapy. However, the olanzapine in monotherapy treated group was not compared with the other groups in terms of efficacy. On the other hand, the univariate statistical methodology which was employed in the previous study did not allow the inclusion of confounding variables.

2. Methods

2.1. Study design

Patients who participated in this study were taken from a phase IV, multicentre, observational, prospective, non-randomized, comparative pharmacoepidemiological study that assessed the effectiveness and safety profile of olanzapine in comparison with other antipsychotics in the hospital setting. The study was conducted in Spain with the participation of 83 inpatient units, located at general hospitals or psychiatric hospitals, from January to September 1999 (Álvarez et al., 2003). A total of 910 patients with a diagnosis of schizophrenia according to the ICD-10 (F.20 of ICD-10 [World Health Organization, 1992]) who had been hospitalized for an acute psychotic episode participated in the study. Patients were included in the study when, after admission, their attending psychiatrist, who was participating in the study, initiated treatment with oral olanzapine or any conventional antipsychotic drug. Those patients to whom treatment with antipsychotic drugs was contraindicated, who were already participating in a clinical trial, or were undergoing treatment with atypical antipsychotics other than olanzapine were excluded from this study.

Indication for treatment was determined solely by clinical judgment, and no restriction was placed on the clinical management of the patients. Treatment could be modified by each participating psychiatrist, and all changes related to dosage or prescription had to be recorded. Patients could be switched from one treatment group to the other by the investigator in case of treatment-emergent adverse events, lack of effectiveness, or due to any other reason. Patients could discontinue the study at any moment.

This study was conducted in accordance with the Declaration of Helsinki (1996). The study protocol was

developed by the sponsor (Lilly S.A., Madrid, Spain) and an advisory group and submitted to the Spanish National Pharmacovigilance Department in compliance with the Spanish legislation. In line with this regulation, neither the approval by ethics committees of the participating hospitals nor patients' signed informed consent were required. However, patients were informed about their privacy protection and the study objectives, and then provided oral consent to participate.

For the purposes of this study, two groups of patients were selected from the above-mentioned sample: the olanzapine in monotherapy group (OGm) and the control group (CG). The OGm was composed of patients receiving olanzapine as the only antipsychotic drug, whereas the CG included those patients treated with one or more conventional antipsychotic (CA) drug. (This way, we could compare the group of patients treated with olanzapine in monotherapy with the group of patients treated with CA, thus controlling for concomitant treatment with olanzapine and CA).

2.2. Assessment instruments

Clinical evaluations were done at baseline and on a weekly basis throughout the whole hospitalization period until a patient was discharged or medication was withdrawn.

Severity of psychotic symptoms was clinically assessed by means of the Clinical Global Impressions-Severity of Illness scale (CGI-S) (National Institute of Mental Health, 1976) that gives a score ranging from 1 (disease-free) to 7 (greatest possible severity), and the Brief Psychiatric Rating Scale (BPRS) (Woerner et al., 1988). The BPRS is a Likert-type scale composed of 18 items that are evaluated by the interviewer, in which each item can be given a score ranging from 0 (absence of symptom) to 6 (extreme severity). Apart from the BPRS total score, the presence of positive, negative, agitation, and depression symptoms was assessed using the BPRS subscales as follows: BPRS positive (conceptual disorganization, suspiciousness, hallucinatory behaviour, and unusual thought content), BPRS negative (emotional withdrawal, motor retardation, blunted affect), BPRS agitation (anxiety, tension, hostility, uncooperativeness, excitement), BPRS depression (feelings of guilt, depressive mood, somatic complaints, anxiety). Behaviour was assessed with the Nurses' Observation Scale for Inpatient Evaluation (NOSIE) (Honigfeld and Klett, 1965).

All adverse events spontaneously reported by the patients or identified by the investigators were recorded. Additionally, EPS (dystonia, hypertonia, hypokinesia, tremor, dyskinesia, and akathisia) were assessed by means of a short questionnaire based on the EPS section of the Udvalg for Kliniske Undersøgelser (UKU) Side Effect Rating Scale (Lingjaerde et al., 1987). Other clinical safety measures such as electrocardiogram, haematology, biochemistry, blood pressure, or weight were monitored whenever the investigators considered them necessary.

Patients were evaluated at baseline and once a week until discharge from hospital.

Treatment response was operationally defined as a decrease of at least 40% from baseline in BPRS total score plus an endpoint BPRS score lower than 18 or an endpoint CGI-S less than 3.

2.3. Statistical analyses

Statistical analyses were made following the "intent-to-treat" principle, taking into account all those patients from whom information had been gathered. This type of analysis includes all patients in the groups to which they were initially assigned, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol. Safety and efficacy measures were assessed at the time of treatment initiation and at discharge. A two-tailed significance level of 0.05 was considered for all tests.

A multivariate approach was carried out to minimize the effect of possible confusing variables when analyzing which factors may have influenced the safety and effectiveness of olanzapine in monotherapy compared with those of conventional antipsychotics.

Parametric (*t*-test) and nonparametric (Wilcoxon) tests were used for the statistical analyses of the continuous variables based on the fulfillment of statistical premises (normality and homoscedasticity) and on the nature of the variable. The chi-squared test, or Fisher's exact test in the event that the chi-squared test could not be applied, was used to analyse the discreet variables. Mean changes on the CGI-S, BPRS, and NOSIE scales was analysed by means of an analysis of variance (ANOVA). Predictors of treatment response and predictors of treatment-emergent EPS were investigated with logistic regression models.

The biometrics department of the MDS Pharma Services (Rosa de Lima, 1, Las Matas 28290, Madrid, Spain) carried out statistical analysis of the study data. The data were simultaneously keyed into two databases by different individuals and later contrasted to eliminate errors. SAS versions 6.12 and 8.1 for Windows (SAS Institute Inc., Cary, NC, USA; Copyright 1997; STAT module) were used for verification, validation, and analysis of the data.

3. Results

3.1. Demographic and clinical characteristics

A total of 724 inpatients treated with olanzapine in monotherapy ($n=339$) or conventional antipsychotics ($n=385$) composed the sample for the present study. Some baseline differences regarding age, length of illness, and several of the clinical rating scores could be observed between the two treatment groups (Table 1). Thus, patients treated with conventional antipsychotics had significantly

Table 1
Baseline sociodemographic and clinical characteristics of the study sample ($N=724$)

Characteristic	OGm ($N=339$)	CG ($N=385$)	p-value
Sex: male, *n* (%)	219 (64.6)	253 (65.7)	0.837[a]
Age (years), mean (S.D.)	35.0 (11.3)	37.4 (11.3)	0.004[b]
Duration of illness (years), mean (S.D.)	10.0 (9.1)	13.3 (9.7)	<0.0001[c]
Schizophrenia subtype: paranoid, *n* (%)	238 (70.2)	291 (75.6)	0.104[a]
Baseline CGI-S score, mean (S.D.)	5.0 (0.8)	5.2 (0.9)	0.0003[d]
Baseline BPRS total score, mean (S.D.)	42.7 (12.0)	45.5 (13.0)	0.004[d]
Baseline BPRS positive score, mean (S.D.)	14.1 (4.4)	15.3 (4.4)	0.0001[d]
Baseline BPRS negative score, mean (S.D.)	7.6 (3.9)	7.0 (4.1)	0.051[d]
Baseline BPRS agitation score, mean (S.D.)	13.2 (6.0)	15.2 (6.2)	<0.0001[d]
Baseline BPRS depressive score, mean (S.D.)	7.9 (4.3)	7.3 (4.1)	0.049[d]
Baseline NOSIE score, mean (S.D.)	44.7 (14.4)	49.4 (16.7)	0.0003[d]
Baseline EPS, *n* (%)	58 (17.1)	59 (15.3)	0.515[a]

Abbreviations: OGm=olanzapine in monotherapy group; CG=control group; CGI-S=Clinical Global Impressions-Severity of Illness scale; BPRS=Brief Psychiatric Rating Scale; NOSIE=Nurses' Observation Scale for Inpatient Evaluation; EPS=extrapyramidal symptoms.
[a] Chi-squared test.
[b] Student's *t*-test.
[c] Wilcoxon test.
[d] ANOVA.

higher scores on the BPRS total ($p=0.004$), positive ($p=0.0001$), and agitation ($p<0.0001$) scales, as well as on the CGI-S ($p=0.0003$) and NOSIE ($p=0.0003$), compared with patients treated with olanzapine in monotherapy, whereas patients treated with olanzapine in monotherapy had a significantly higher score on the BPRS depressive scale ($p=0.049$) and a trend toward a higher score on the BPRS negative scale ($p=0.051$).

Haloperidol was the most frequently prescribed antipsychotic in the CG, with 291 (75.6%) patients taking this drug as first prescription. The doses of olanzapine and haloperidol used throughout the study are shown in Table 2. The initial dose refers to the one prescribed at baseline, whereas the mean dose was calculated based on the mean dose that each patient received throughout the study period. The final dose refers to the one prescribed at the time of discharge or end of follow-up. Finally, the modal dose was defined as the daily dose of the drug most frequently prescribed throughout the study period. Mean duration of the study was 21.24 days (S.D.=13.55) in the olanzapine group and 21.19 days (S.D.=13.88) in the conventional antipsychotics group.

Table 2
Initial, mean, final, and modal doses of olanzapine and haloperidol during the study period

Type of dose	Type of statistic	Olanzapine ($n=339$)	Haloperidol ($n=291$)
Initial doses (mg)	Mean (S.D.)	14.1 (6.0)	15.4 (8.6)
	Median	10.0	15.0
	Range	2.5–30.0	1.5–50.0
Mean doses (mg)	Mean (S.D.)	16.5 (5.7)	16.7 (8.9)
	Median	16.7	15
	Range	5–32.5	2.7–58.1
Final doses (mg)	Mean (S.D.)	17.3 (6.2)	15.3 (9.4)
	Median	20.0	13.5
	Range	5.0–30.0	0.9–60.0
Modal doses (mg)	Mean (S.D.)	16.6 (6.6)	16.9 (10.3)
	Median	20.0	15.0
	Range	2.5–30.0	0.9–75.0

A total of 37 (10.9%) patients from the olanzapine group and 49 (12.7%) from the control group prematurely discontinued their participation in the study. No significant differences between the two groups could be observed regarding the reasons for discontinuation. A significantly higher percentage of patients in the OGm than in the CG received concomitant treatment with benzodiazepines (56.0% vs. 44.7%, $p=0.003$) whereas concomitant use of antidepressants and mood stabilizers was balanced (6.5% vs. 4.2%, and 3.8% vs. 4.2% respectively). However, concomitant use of anticholinergic drugs was much more frequent in the CG (52.2% vs. 8.3%, $p<0.001$).

3.2. Safety

General adverse events were more common in the CG than in the OGm (55.8% vs. 24.8%, $p<0.001$). Somnolence was reported at a similar rate both in the OGm and CG (2.8% vs. 2.9%), and weight gain was reported more commonly in the OGm than in the CG (2.0% vs. 0.2%; Fisher's exact test, $p=0.03$).

No significant differences were observed with respect to the presence of EPS at the beginning of the study between the patients in the OGm and in the CG (17.1% vs. 15.3%). Considering individual EPS at baseline, statistically significant differences were only observed for the presence of hypokinesia with a higher percentage of patients in the OGm than in the CG showing this symptom (9.7% vs. 5.5%, $p=0.029$).

As shown in Table 3, treatment-emergent EPS, or worsening of preexisting ones, were statistically significantly more frequent in the CG compared with the OGm (39.0% vs. 11.2%, $p<0.0001$). When all the individual EPS (dystonia, hypertonia, hypokinesia, tremor, akathisia, and dyskinesia) were considered separately, the differences

Table 3
Presence of extrapyramidal symptoms associated with antipsychotic treatment[a]

Type of EPS	OGm (N=339)		CG (N=385)		p-value[b]
	n	%	n	%	
Extrapyramidal symptoms, general	38	11.2	150	39.0	<0.0001
Individual symptoms					
Dystonia	6	1.8	36	9.4	<0.0001
Hypertonia	6	1.8	54	14.0	<0.0001
Hypokinesia	12	3.6	55	14.3	<0.0001
Tremor	16	4.8	58	15.1	<0.0001
Akathisia	7	2.1	50	13.0	<0.0001
Dyskinesia	0	0.0	12	3.1	0.001
Others	8	2.4	8	2.1	0.792

Abbreviations: EPS=extrapyramidal symptoms; OGm=olanzapine in monotherapy group; CG=control group.
[a] This table covers both treatment-emergent EPS and worsening of preexisting ones.
[b] Chi-squared test.

between the two groups remained significant for all the symptoms ($p<0.001$ for all the comparisons).

Since several differences were observed for some baseline demographic and clinical characteristics between the two groups, a logistic regression analysis was used to more adequately assess the factors that could have been influencing the emergence of EPS. The following variables were included as candidates for this analysis: schizophrenia subtype, baseline scores on severity scales, presence of baseline EPS, duration of illness, and treatment strategy (olanzapine in monotherapy or conventional antipsychotics). Treatment strategy was the only variable that was significantly correlated with the emergence of new EPS or worsening of preexisting ones (R.R.=5.04; [95% CI, 3.39–7.48]; $p<0.0001$). Thus, patients treated with conventional antipsychotics presented five times the risk of developing EPS than patients treated with olanzapine in monotherapy.

To assess the potential role of antipsychotic dosage in the risk of treatment-emergent EPS, a new logistic regression analysis was performed including doses of olanzapine and haloperidol (the most frequently prescribed antipsychotic drug in the CG) in the model. Treatment strategy remained significantly associated with EPS (R.R.=5.27; [95% CI, 3.48–7.98]), whereas the antipsychotic dosage appeared not to be correlated with treatment-emergent EPS (R.R.=1.02; [95% CI, 0.86–1.21]; $p=0.83$) (Figs. 1 and 2).

3.3. Effectiveness

Olanzapine was significantly superior to conventional antipsychotics in lowering the BPRS negative ($p=0.0002$) and depressive ($p=0.002$) scores (Table 4). No significant differences between the two groups could be observed for the mean difference in the BPRS total, positive, and agitation scores. The mean improvement on the CGI-S scale and mean reduction on the NOSIE scale did not significantly differ between the two groups (Table 4).

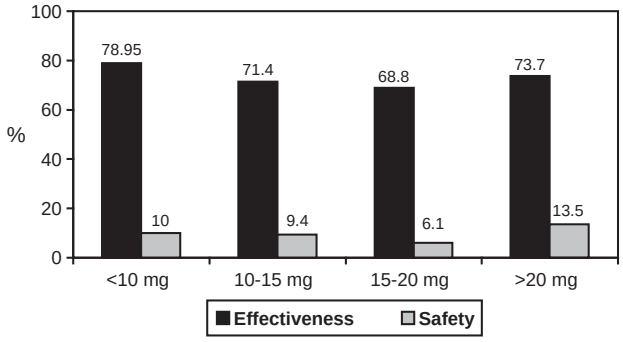

Fig. 1. Safety and effectiveness of olanzapine by modal dose (N=339). Effectiveness: Percentage of patients obtaining a clinical response (operationally defined as a decrease of at least 40% from baseline in BPRS total score plus an endpoint BPRS score lower than 18 or less than on the CGI-S scale). Safety: Percentage of patients with treatment-emergent EPS.

A more robust measure of treatment effectiveness can be obtained by calculating "clinical response", previously defined in our study as a decrease of at least 40% in the baseline BPRS score plus an endpoint CGI-S of 3 or less or an endpoint BPRS<18. Following these criteria, response rates for the olanzapine group were 72.9% compared with 63.0% for the control group, this comparison being statistically significant ($p=0.005$).

Using a similar methodology as for the safety analyses, a logistic regression analysis was carried out to assess the factors that could be influencing clinical response to treatment. Variables included in the analysis were: schizophrenia subtype, baseline scores on severity scales, duration of illness, and treatment strategy (olanzapine in monotherapy or conventional antipsychotics). Treatment strategy was the only variable significantly associated with clinical response (R.R.=0.63; [95% CI, 0.46–0.87]; $p=0.005$). Thus, patients treated with conventional antipsychotics had somewhat more than half the probability of obtaining clinical response than patients treated with olanzapine in monotherapy.

The influence of the antipsychotic dosage on clinical response was also investigated with a new logistic

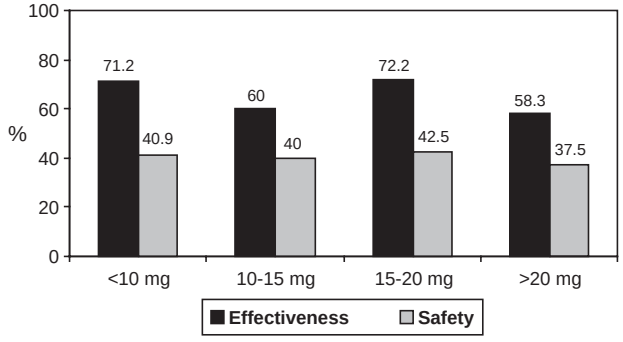

Fig. 2. Safety and effectiveness of haloperidol by modal dose (N=291). Effectiveness: Percentage of patients obtaining a clinical response (operationally defined as a decrease of at least 40% from baseline in BPRS total score plus an endpoint BPRS score lower than 18 or less than on the CGI-S scale). Safety: Percentage of patients with treatment-emergent EPS.

Table 4
Change in CGI-S, BPRS, and NOSIE scores in each treatment group

	OGm (n=339)	CG (n=385)	p-value[a]
CGI-S, mean improvement (S.D.)	1.8 (1.1)	1.7 (1.1)	0.719
BPRS total, mean improvement (S.D.)	27.3 (13.5)	27.0 (14.0)	0.711
BPRS positive, mean improvement (S.D.)	9.1 (5.0)	9.2 (5.1)	0.853
BPRS negative, mean improvement (S.D.)	3.6 (3.2)	2.7 (3.4)	0.0002
BPRS agitation, mean improvement (S.D.)	9.7 (6.1)	10.4 (6.5)	0.114
BPRS depressive, mean improvement (S.D.)	5.1 (3.6)	4.2 (3.5)	0.002
NOSIE, mean improvement (S.D.)	19.4 (13.5)	20.9 (16.8)	0.222

Abbreviations: CGI-S=Clinical Global Impressions-Severity of Illness scale; BPRS=Brief Psychiatric Rating Scale; NOSIE=Nurses' Observation Scale for Inpatient Evaluation; OGm=olanzapine in monotherapy group; CG=control group.
[a] ANOVA.

regression analysis with the same methodology used for the safety analyses. Again, treatment strategy remained significantly associated with clinical response (R.R.=0.67; [95% CI, 0.47–0.95]), whereas the antipsychotic dosage failed to show any significant association with response to treatment (R.R.=0.93; [95% CI, 0.79–1.08]; p=0.35) (Figs. 1 and 2). Although not statistically significant (Table 2), a tendency to increase antipsychotic dose could be observed in those patients treated with olanzapine in monotherapy, whereas this tendency could not be observed in the group of patients treated with conventional antipsychotics.

4. Discussion

To our knowledge this is the largest prospective study conducted with an atypical antipsychotic in the hospital setting. However, as already pointed, several limitations of observational studies should be mentioned before proceeding to the discussion of the main findings: (1) selection bias due to lack of randomization, (2) probable underreporting of adverse events compared with clinical trials, and (3) confounding effects of frequent use of concomitant medications.

The first of the above-mentioned limitations is probably the most problematic one, as we must assume that the demographic and clinical variables differed between the two treatment groups. We have tried to minimize this limitation by comparing not only the endpoint scores, but also the *difference* between endpoint and baseline scores in all the assessment instruments. Moreover, we have carried out logistic regression analyses including possible confusing variables to more reliably study the factors that could influence the safety and effectiveness of these drugs. Regarding the second limitation, in our opinion, it would be logical to assume that the probable underreporting of adverse events occurred equally in both treatment groups, so the comparisons should not therefore be greatly affected. The third limitation refers to the use of concomitant medication. In our study, however, the only significant difference between both treatment groups concerned the use of anticholinergic drugs, which are prescribed to treat treatment-emergent EPS. As it may be argued that olanzapine-treated patients with more severe positive or agitation symptoms received concomitant conventional antipsychotics and that these latter drugs could have been responsible for the reduction of these symptoms, we have excluded those patients from our analyses, thus minimizing this possibly confusing factor.

The main objective of this study was to evaluate the safety and effectiveness of patients treated with olanzapine, when used in monotherapy, compared with conventional antipsychotics in the treatment of patients with schizophrenia hospitalized due to a psychotic episode. A previous report on the whole sample from which this cohort was extracted showed that olanzapine (in monotherapy or with concomitant conventional antipsychotics), compared with conventional antipsychotics, had less EPS and experienced greater improvement in BPRS total, positive, negative, agitation, and depression scores (Álvarez et al., 2003). When the subgroup of patients with first-episode schizophrenia was selected, the same results were obtained regarding the lower incidence of EPS and the higher effectiveness of olanzapine in reducing the BPRS total as well as positive, negative, agitation, and depression scores (Bobes et al., 2003). However, the possible influence on effectiveness of the concomitant conventional antipsychotics could not be ruled out in any of the previous studies. In addition, the potential influence of the antipsychotic dosage on safety and effectiveness issues was not addressed.

A relatively high number of patients (N=724) were included in the present study, and the retention rate was also high (88.2%). The mean dose of olanzapine prescribed in this study was 16.5 mg/day, higher than the mean dose of 13.0 mg/day used in an observational study in patients with schizophrenia conducted in the outpatient setting in Spain in 1998 (Gomez et al., 2000). The mean dose of haloperidol was also relatively high (16.7 mg/day). However, we consider that it is not appropriate to compare these results with those of controlled clinical trials, as the conditions of these trials require that the investigators keep their patients under strict protocol limits. We estimate that our data reflect the routine clinical practice with hospitalized schizophrenic patients in Europe.

At baseline, patients treated with olanzapine were significantly younger, had a shorter illness duration, and more prominent depressive and negative symptoms compared with those treated with conventional antipsychotics. On the other hand, patients treated with conventional antipsychotics had a CGI-S score and more prominent positive and agitation symptoms than those treated with olanzapine. In our opinion, these data reflect the routine clinical practice of Spanish psychiatrists in 1999, only approximately a year after the introduction of olanzapine in Spain. At that time, patients with more severe symptoms of schizophrenia tended to be treated with conventional antipsychotics, to which most psychiatrists were much more used, leaving the "newly" introduced olanzapine to those younger patients who mainly presented with negative and depressive symptoms.

4.1. Safety

Our safety results among those patients treated with olanzapine in monotherapy are consistent with the safety profile shown in the registration clinical trials and included in the product's package insert. Somnolence and weight gain are among the most commonly reported adverse events in patients treated with olanzapine. The rate of somnolence was very low in both groups (OGm: 2.8% and CG: 2.9%), particularly if we take into account that around 50.0% of the patients received concomitant treatment with benzodiazepines. Weight gain was more commonly observed in the group of patients treated with olanzapine, but only in 2% of these patients. However, no conclusions regarding olanzapine's association with weight gain can be drawn from a short-term study in the hospital setting as the present one. We consider that the issue of weight gain associated with antipsychotic treatment must be addressed in prospective long-term studies.

Concerning treatment-emergent EPS, we observed a clear advantage for patients treated with olanzapine compared with conventional antipsychotics. The incidence of any extrapyramidal symptom during the hospital stay was significantly lower in the olanzapine group compared with the control group ($p<0.0001$). The incidence of specific EPS (dystonia, hypertonia, hypokinesia, tremor, dyskinesia, and akathisia) in olanzapine-treated patients was also significantly lower ($p<0.001$) compared to patients treated with conventional antipsychotics. In the control group, up to 39.0% of patients had at least one treatment-emergent EPS during the study, even considering that up to 52.2% of the patients from this group were receiving anticholinergic drugs. On the other hand, wide use of anticholinergic drugs may negatively correlate with safety and tolerability since they are associated with poor cognitive function and, especially relevant in older patients, with anticholinergic side effects (constipation, urinary retention, sedation).

When a multivariate methodology was employed, our results showed that patients treated with conventional antipsychotics had, regardless of antipsychotic dosage, five times the risk of developing EPS than patients treated with olanzapine.

In this study, patients received the doses of antipsychotics that their doctors considered optimal in terms of the effectiveness/tolerability ratio. Thus, we were also interested in studying whether the dosage of olanzapine and conventional antipsychotics correlated with treatment-emergent EPS. A new logistic regression analysis was carried out introducing antipsychotic dosage as a candidate. Again, the only variable that appeared to be significantly associated with treatment-emergent EPS was treatment strategy, with no significant correlation with antipsychotic dosage. The finding that dosage of conventional antipsychotics was not correlated with treatment-emergent EPS is contrary to other published studies (Casey, 1991) and needs further examination in future studies.

4.2. Effectiveness

When interpreting the effectiveness results, we should take into account several factors. Firstly, there were significant differences at baseline in most of the clinical evaluations (BPRS total, positive, agitation, and depressive subscores, and CGI-S). As, from a statistical point of view, our data did not allow to carry out an analysis of covariance adjusting for baseline scores, we chose an intermediate approach, comparing the difference between the endpoint and baseline score (which, in any case, is an adjustment for the baseline score). Secondly, the unblinded approach of this naturalistic study represents an important limitation for the interpretation of results extracted from subjective assessment instruments (BPRS, CGI-S, NOSIE). Unfortunately, we cannot determine to what extent this issue may have biased the results in favour of olanzapine. Finally, we should consider that baseline symptom severity was significantly higher in the group of patients treated with conventional antipsychotics for most of the scores (BPRS total, positive, agitation; CGI-S; and NOSIE) with a $p<0.004$ in all of them, whereas the group of patients treated with olanzapine showed higher baseline scores only for BPRS depressive ($p=0.049$) and negative ($p=0.051$) subscales. It is usually considered that the higher the baseline clinical values are, the greater improvement may be shown. In fact, we have confirmed in our study that those patients with greater baseline BPRS scores had a greater proportional decrease on BPRS. Thus, it can be argued that, in any case, these baseline differences would influence the results in favour of conventional antipsychotics. Patients treated with olanzapine in monotherapy had a significantly higher improvement on their negative and depressive symptoms than those treated with conventional antipsychotics. Although these results should be considered cautiously due to the baseline differences, they are consistent with previous findings on the depressogenic nature of conventional antipsychotics (Mortimer et al., 2003; Wheeler-Vega et al., 2003) and the poorer effectiveness of conventional antipsychotics compared to

olanzapine in the treatment of negative symptoms in schizophrenia (Beasley et al., 1996; Collaborative Working Group on Clinical Trial Evaluation, 1998).

Clinical treatment response was significantly more frequent in olanzapine-treated patients than in those who received conventional antipsychotics ($p=0.005$). This measure has the advantage of selecting those patients who, while decreasing their global symptomatology, completed the study with a relatively low level of severity of illness. This way, we are not considering as treatment responders those patients who either had a low level of symptom severity from the beginning to the end of the study with little or no change at all, or those who showed an improvement but remained with a high symptom severity at the end of the follow-up period.

Again, when a multivariate methodology was employed, our results showed that patients treated with olanzapine had, regardless of antipsychotic dosage, around one and a half more chance of responding to treatment than patients treated with conventional antipsychotics.

4.3. Conclusions

In summary, in this large observational study with an unselected sample of acutely psychotic inpatients with schizophrenia olanzapine, as antipsychotic monotherapy, was better tolerated (in terms of EPS) and more effective (in terms of clinical response), than a sample of patients treated with conventional antipsychotics.

Acknowledgments

Lilly Research Laboratories, Alcobendas, Spain, sponsored this work.

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