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Safety of olanzapine versus conventional antipsychotics in the treatment of patients with acute schizophrenia. A naturalistic study

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Abstract

Background: Conventional antipsychotics although effective in treating acute psychotic and behavioural symptoms are subject to certain limitations due to the high incidence of side effects associated, mainly extrapyramidal symptoms (EPS), and insufficient response shown in some cases. EPS are a major factor in neuroleptic non compliance and high relapse rates among patients. This study was designed to assess the safety and effectiveness of olanzapine compared to typical antipsychotics drugs in the treatment of schizophrenic inpatients at acute psychiatric in-patient units. *Method:* Data from 904 patients schizophrenic patients (F20 of ICD10, WHO) were collected in this prospective, comparative, non-randomized, open and observational study. Patients were followed during their entire hospital stay. Safety was assessed through the collection of spontaneous adverse events and a specific extrapyramidal symptoms questionnaire (EPS). Clinical status was measured through the Brief Psychiatric Rating Scale (BPRS), Clinical Global Impression of Severity (CGI-S), Patient Global Impression of Improvement (PGI) and the Nursing Observational Scale for In-patient Evaluation (NOSIE). *Results:* A total of 483 patients received olanzapine (olanzapine group, OG), and 421 received typical antipsychotics (control group, CG). Treatment emergent EPS, or worsening of previous EPS were statistically significantly higher in the CG ($P=0.001$). Responder rate was statistically greater in the OG ($P<0.001$). Mean change in BPRS-total, BPRS-negative, BPRS-agitation subscales and PGI was significantly higher in the OG ($P<0.001$). Mean decrease in CGI, BPRS positive and BPRS depression sub-scales was also significantly lower ($P\leq0.05$). Mean change in the NOSIE scale was similar between both groups. *Conclusion:* Olanzapine has been shown to be better tolerated in comparison with conventional antipsychotics in a large unselected sample of acutely psychotic schizophrenic in-patients. Its effectiveness may be greater than that of conventional antipsychotics.

Keywords: Schizophrenia; In-patients; Olanzapine; Antipsychotics; Safety; Effectiveness

1. Introduction

Conventional antipsychotics have permitted a majority of schizophrenic patients to be treated in the community and the role of hospital admission has changed enormously

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since the pre-neuroleptic era. Currently, psychiatric hospitalisation of schizophrenic patients is usually indicated for the management of acute psychotic episodes that could not be managed within the outpatient setting. The role of conventional antipsychotics in this setting is to rapidly reduce psychotic and behavioural symptoms, allow an early discharge and set the stage for the post-admission long-term management of the disorder.

Nevertheless, these conventional antipsychotics are subject to certain limitations for the optimal management of acute psychotic patients. A high percentage of schizophrenic patients present an insufficient response to treatment with this conventional antipsychotic medication (Brenner et al., 1990) and up to 60% relapse 1 year after therapy (Kane, 1996). Moreover, the high incidence of side effects associated with conventional antipsychotic drugs, particularly the extrapyramidal symptoms (EPS), greatly contribute to patients' discomfort during their admissions and make patients more reluctant to maintain antipsychotic treatment. EPS are a major factor in neuroleptic non compliance and high relapse rates among patients (Weiden et al., 1986). All of these factors contribute to repeated hospital admissions and to progressive social and occupational dysfunction. In this sense, drugs that would have both high effectiveness and good tolerability could be of great help for the management of acute psychotic episodes and facilitate the transition between the acute in-patient care and long-term out-patient care.

The safety and efficacy of olanzapine have been studied in various placebo-controlled clinical trials (Beasley et al., 1996a,b) as well as in trials controlled with haloperidol (Tollefson et al., 1997) and risperidone (Tran et al., 1997).

There were no treatment-emergent adverse events that occurred statistically significantly more frequently with olanzapine-treated patients compared with placebo-treated patients (Beasley et al., 1996a). Treatment-emergent adverse events that occurred statistically significantly more frequently with olanzapine compared to haloperidol were excessive appetite and dryness of mouth. (Tollefson et al., 1997). In comparison with haloperidol and risperidone, olanzapine has been temporally associated with a lower incidence of extrapyramidal symptoms and a lower incidence of increased prolactin (Tollefson et al., 1997; Tran et al., 1997).

The results of the clinical trials should be confirmed by means of effectiveness studies in daily clinical practice. This is particularly so in disorders such as schizophrenia where the experimental situation of a clinical trial is often substantially different from daily clinical practice (Collaborative Working Group on Clinical Trial Evaluations, 1998). Most clinical trials with antipsychotic drugs exclude patients with concomitant organic or psychiatric disorders, particularly disorders relating to substance abuse/dependence (Collaborative Working Group on Clinical Trial Evaluations, 1998), highly prevalent conditions in the population with schizophrenia (Buckley, 1998). In the same way, the limitations on the concomitant use of other antipsychotic drugs is another factor that contributes to this distance between the experimental situation and daily clinical practice.

The main objective of the study was the assessment of olanzapine's safety (particularly the presence of extrapyramidal symptoms) and effectiveness in a cohort of in-patients acutely admitted in psychiatric units and treated under normal usage conditions, when compared with another cohort treated with conventional antipsychotic drugs.

2. Subjects and methods

2.1. Subjects

Data from nine hundred and ten subjects were collected in 83 participating centers from January to September 1999. Schizophrenic patients (F.20 of ICD10, World Health Organisation) (WHO, 1994) hospitalised because of an acute psychotic episode could enter this study when an oral antipsychotic medication either with olanzapine or with a conventional antipsychotic treatment was started following admission. Patients included in clinical trials or under treatment with atypical antipsychotic medications other than olanzapine (clozapine, risperidone, quetiapine or sertindole) could not participate as well as those patients in whom antipsychotic drug therapy was contraindicated.

The study protocol was developed by the sponsor and an external advisory group created for this study (Drs Alvarez, Bobes, Carrasco, Cañas, Gascón, Gibert and Gutierrez). The protocol was submitted to the Spanish National Pharmacovigilance Department in compliance with Spanish legislation applicable to non-experimental observational studies. In line with this regulation, no approval by Ethics Committees of the participating centers nor patient-signed informed consent were required to be obtained prior to the commencement of the study. Nevertheless, investigators informed the patients about the objectives of the study and then, oral consent to participate was obtained. Patients' confidentiality was kept as no details were reflected in the study documentation.

All patients were included in 83 acute in-patient units at General Hospitals or at Psychiatric Hospitals. The participating sites were selected by the sponsor in consultation with the advisory group, combining criteria of size and geographical distribution. Selected sites represent more than 40% of psychiatric acute in-patient units in the country, evenly spread across the Spanish territory.

2.2. Methods

2.2.1. Treatments

Investigators were asked to include appropriate participants in a consecutive and naturalistic fashion; the first oral

medication prescribed at the moment of the admission (olanzapine or conventional antipsychotics) determined the group to which the patient was allocated. Investigators were instructed to use their routine clinical judgment in choosing treatments in order to avoid the mentioned problems of controlled trials. Thus, two different groups were considered: the olanzapine group (OG), with patients receiving olanzapine alone or in combination with typical antipsychotic drugs and the control group with typical antipsychotic drugs (CG) with patients receiving one or more medications from the aforementioned therapeutic groups. In order to limit selection bias, participant psychiatrists were asked to include all eligible patients until completing a block with six patients on each medication group.

Once a patient was participating, prescribed treatment could be modified following clinical needs and all the changes related to dosage or prescription should be recorded. Patients could be switched from one group to the other following investigator's best judgment in the case of lack of efficacy, adverse effects or due to other reasons. Patients were followed up throughout the whole hospitalisation period until definitive discharge.

Severity of psychotic symptoms was clinically evaluated at admission by means of the Clinical Global Impression (CGI) severity scale (National Institute of Mental Health, 1976) and the Brief Psychiatric Rating Scale (BPRS) (Woerner et al., 1988) together with BPRS positive (conceptual disorganization, suspiciousness, hallucinatory behaviour, unusual thought content), BPRS negative (emotional withdrawal, motor retardation, blunted affect), BPRS agitation (anxiety, tension, hostility, uncooperativeness, excitement) and BPRS depression (guilt feelings, depressive mood) subscales. See Table 1 for the BPRS items considered for the analyses of the BPRS subscales. Behaviour was assessed with the NOSIE scale (Honigfeld and Klett, 1965). Patients were evaluated weekly during the study with the mentioned scales along with the Patient Global Impression (PGI) of change scale (National Institute of Mental Health, 1976). Extrapyramidal symptoms were evaluated using a short questionnaire based on the extrapyramidal symptoms section of the UKU scale (Lingjaerde et al., 1987) (dystonia, hypertonia, hypokinesia, tremor, dyskinesia, and akathisia). Evaluations were carried forward on a weekly basis until discharge or discontinuation. Other safety assessments were conducted by clinicians as necessary. Patients could withdraw their participation at any point of the study.

Treatment-response was defined as according to the following criteria: baseline-endpoint decrease in BPRS total score $\geq$40% plus and endpoint BPRS score $<$18 or an endpoint CGI score $\leq$3.

The study was monitored by an external Clinical Research Organization (MDS, Madrid, Spain). Monitoring activities included initial training sessions, quality control of 100% of case report forms prior to data entry, telephone monitoring on all sites and monitoring visits with source data verification on 55% of the sites.

2.2.2. Statistics

The study was designed with the aim of detecting the differences in the incidence of extrapyramidal symptoms between the olanzapine group and the control group, with a 90% power and a two-tailed α risk of 0.05; thus, being considered a 38% incidence of EPS for the olanzapine group and a 50% for the control group, a sample size of approximately 400 patients was estimated for each group. Additionally, effectiveness analysis was conducted, this analysis was exploratory since this study was not designed to investigate specifically this issue.

The biometrics department of Phoenix International has carried out the statistical analysis. The system used for the verification, validation and analysis of the data was SAS®

Table 1
Demographic and clinical characteristics of the sample at baseline

Characteristics		Olanzapine N=483	Control group N=421	Statistics	P-value
Age (years)	Mean (S.D.)	35.3 (11.1)	37 (11.4)	Wilcoxon, Z=2.416	0.016
Gender (% males)		67.2	66.5	χ^2=0.04	0.838
Time from onset (years)	Mean (S.D.)	10.6 (9.3)	12.9 (9.7)	Wilcoxon, Z=3.947	<0.001
No. of previous hospitalizations	Mean (S.D.)	4.1 (6.4)	4.3 (6.1)	Wilcoxon, Z=0.39	0.694[a]
Baseline CGI Score	Mean (S.D.)	5.06 (0.83)	5.24 (0.85)	Wilcoxon, Z=3.41	<0.001
Baseline BPRS	Mean (S.D.)	43.2 (12.2)	45.6 (13.1)	Wilcoxon, Z=2.74	0.006
BPRS positive Items 4, 11, 12, 15	Mean (S.D.)	14.1 (4.4)	15.4 (4.5)	Wilcoxon, Z=4.09	<0.001
BPRS negative Items 3, 13, 16	Mean (S.D.)	7.4 (3.9)	7.1 (4.2)	Wilcoxon, Z=−1.28	0.200
BPRS agitation Items 2, 6, 10, 14, 17	Mean (S.D.)	13.9 (6.2)	15.1 (6.2)	Wilcoxon, Z=−3.19	0.001
Baseline NOSIE	Mean (S.D.)	45.73 (14.85)	49.07 (16.66)	Wilcoxon, Z=2.90	0.004
Baseline EPS (%)		36.0	34.7	χ^2=0.18	0.673

[a] Overall P-value.

version 6.12 for Windows (SAS Institute Inc., 1997, STAT module).

The analysis has been carried out on the basis of 'intention to treat' principle, with the result that all patients for whom information was available have been included. Six patients were excluded for the analysis: five were initially considered for the study but were not included since they were on treatment with clozapine and did not meet the entry criteria, and one with no treatment group defined.

Statistical analyses have been carried out, following the LOCF approach, for all time-points except on those cases in which patients switched from one group to the other, and in whom analysed data have been considered until the switching point.

For the statistical analysis of continuous variables, parametric and non-parametric tests have been used depending on applicability constraints (normality and homoscedasticity) and the nature of the variable. Mean change in the CGI, BPRS and NOSIE scales has been analysed by means of an ANCOVA test (in this cases, adjusted means are provided). To analyse discrete variables, the χ^2-test or Fisher's Exact test have been used. We have considered a two-tailed significance level of 0.05 for all tests. Adjustments have been performed in relevant clinical and demographic variables where baseline differences have been found (schizophrenia type, baseline value, and duration length).

3. Results

3.1. Demographic and clinical characteristics

No randomisation was performed following the naturalistic setting of the study. Data from 483 (53.4%) patients assigned to the OG were compared to those of 421 (46.6%) patients in the CG.

Patient population between-groups showed statistically significant differences concerning some of the baseline demographic or clinical characteristics such as mean age and length of illness. Although globally more male patients were included (66.9% vs. female 33.1%), distribution between both groups was balanced. No differences related to medical conditions, schizophrenia subtypes, previous number of admissions or length of hospitalisations were found (Table 1).

Haloperidol was the most frequently prescribed drug among the conventional antipsychotic medication on the control group (76.25%), followed by levopromazine (23.75%) and zuclopenthixol (13.54%): as observed, total percentage is above 100% since about 42% of the CG patients received combined antipsychotic therapy.

Rating scores at admission for the CGI, BPRS positive sub-scale and NOSIE scales showed poorer results on the CG compared to the OG; those differences were statistically significant (Table 1).

Olanzapine and haloperidol mean and median doses used throughout the study are presented in Table 2. Initial dose is that prescribed at baseline, while mean dose is calculated from the mean dose received by each patient during the study. Final dose refers to the dose prescribed at discharge or end of follow-up, whatever occurred first.

Seventeen patients in the olanzapine group (3.5%) switched to the other treatment group against 37 patients (8.8%) in the control group. The main reason for switching was lack of efficacy on both groups (2.7% OG vs. 2.9% CG); nevertheless, adverse events were only present in the CG (2.6 vs. 0.0% OG) as reason for treatment change.

The drop out rate is presented in Table 3 describing the different reasons. One patient with a previous history of untreated chronic obstructive lung disease and auricular flutter died in the OG due to acute respiratory depression in relation to a respiratory infection. The event was considered unrelated to the study drug by the treating physician. No significant differences between groups were observed.

3.2. Concomitant medication

More patients in the CG received acute parenteral medication at admission in comparison with the OG (15.6 vs. 26.2%, $P=0.001$). A higher percentage of patients received benzodiazepines as co-prescriptions in OG (67.7 vs. 56%); also antidepressants and mood stabilisers were more frequent in the OG (5.6 vs. 1.9% and 5.4 vs. 3.8%, respectively), whereas anticholinergic medication use was much higher in the CG (59.1 vs. 15.5%).

Olanzapine was combined with conventional antipsychotics in 26.5% of the cases at initiation of treatment (high potency 16.8%, low potency 12.2%) and 24.5% at endpoint (high potency 15.7%, low potency 11.8%), while 50.2% of the patients that received haloperidol also received additional conventional antipsychotics initially (high potency 10%, low potency 43%) and 49.3% at endpoint (high potency 16.6%, low potency 38.3%).

3.3. Emergent adverse events

Treatment emergent EPS, or worsening of previous EPS were statistically significantly higher in the CG compared

Table 2
Initial and final dose of olanzapine and haloperidol in the study

		Olanzapine $N=483$	Haloperidol $N=321$
Initial dose	Mean (S.D.)	14.4 (6.1)	15.4 (8.7)
	Median	10	15
	Range	2.5–30	1.5–50
Final dose	Mean (S.D.)	17.7 (6.4)	15.3 (9.4)
	Median	20	13.5
	Range	5.0–40	0.9–60

Table 3
Reason for discontinuation from the study by treatment group

	Olanzapine $N=483$		Control group $N=421$		Statistics	P-value
	n	%	n	%		
Protocol completed						
Total	416	87.6	355	87.4	$\chi^2=0.004$	0.950
Discontinuation[a]						
Details						
Investigator decision	24	5.0	23	5.5		
Patient decision	4	0.8	7	1.7		
Patient discharge[b]	7	1.4	5	1.2		
Death	1	0.2	0	0.0		
Lost to follow-up[c]	14	2.9	11	2.6		
Other	8	1.7	5	1.2		
Total	59	12.4	51	12.6	$\chi^2=2.78$	0.733

[a] Overall P-value.
[b] The category 'patient discharge' includes those patients who escaped or left institution prematurely.
[c] The category 'lost to follow-up' includes those patients who did not have a final evaluation available.

to the OG (44.5 vs. 16.4%, $P=0.001$); some extrapyramidal symptoms present in the CG, when collected by means of the questionnaire, were statistically significantly more frequent if compared with the OG, especially dyskinesia (Table 4). No baseline differences were observed between treatments. These data were corroborated by extrapyramidal adverse events reported spontaneously (CG 49.5 vs. OG 19%, $P=0.001$).

More adverse events were present in the CG than in the OG (55.8 vs. 27.3%, $\chi^2=75.71$, $P=0.001$). Table 5 presents an adverse effects listing classified and coded according to the COSTART dictionary (US Department of Health and Human Services, 1995). No leukopenia was reported.

The sub-analysis performed in the OG, olanzapine in monotherapy (O-mon) versus olanzapine combined with conventional antipsychotic (O-com), with regard to the treatment emergent EPS and general adverse events reported throughout the study, showed statistically significant differences between these two sub-groups in the case of emergent EPS (O-mon: 13.6% vs. O-com: 24.2%, $P=0.005$). These two groups, when analyzed separately, were still at a lower risk for EPS than the control group ($P\leq0.0001$).

No statistical difference was found for general adverse events (O-mon: 24.8% vs. O-com: 34.4%, $P=0.037$) (Table 5).

3.4. Effectiveness

The criteria for treatment efficacy was the relative change from baseline in BPRS (at least 40% reduction) plus endpoint CGI=3 or endpoint BPRS<18; following these criteria and up to the switch time-point, responder rates for the olanzapine group were 71.9% (340 patients) compared to 58.7% (244 patients) for the control group: this comparison was statistically significant ($\chi^2=17.18$, $P=0.001$) even with adjusted values by type of schizo-

Table 4
Treatment emergent extrapyramidal symptoms

	Olanzapine group $N=483$		Control group $N=421$		Statistics	P-value
	n	%	n	%		
EPS	79	16.4	187	44.5	$\chi^2=85.43$	0.001
Individual EPS						
Dystonia	9	1.9	47	11.22	$\chi^2=33.50$	0.001
Hypertonia	20	4.1	73	17.4	$\chi^2=42.49$	0.001
Hypokinesia	28	5.8	80	19.0	$\chi^2=37.32$	0.001
Tremor	25	5.2	78	18.6	$\chi^2=39.75$	0.001
Akathisia	16	3.3	69	16.4	$\chi^2=45.19$	0.001
Dyskinesia	3	0.6	17	4.0	Fisher	<0.001
Others	9	1.9	10	2.4	$\chi^2=0.29$	0.755

Table 5
Treatment-emergent adverse events according to the COSTART dictionary

	Olanzapine group						Control group Total $N=421$	
	Olanzapine-monotherapy $N=355$		Olanzapine combined $N=128$		Olanzapine Total $N=483$			
	n	%	*n*	%	*n*	%	*n*	%
Akathisia	13	3.7	10	7.8	23	4.8	75	17.8
Anxiety	4	1.1	4	3.1	8	1.7	7	1.7
Asthenia	11	3.1	4	3.1	15	3.1	22	5.2
Dry mouth	7	2.0	5	3.9	12	2.5	16	3.8
Dystonia	4	1.1	4	3.1	8	1.7	43	10.2
Extrapyramidal syndrome[a]	1	0.3	3	2.3	4	0.8	16	3.8
Hypertonia	14	3.9	13	10.2	27	5.6	81	19.2
Hypokinesia	23	6.5	21	16.4	44	9.1	92	21.9
Somnolence	10	2.8	6	4.7	16	3.3	12	2.9
Tremor	24	6.8	8	6.3	32	6.6	98	23.3
Weight gain	7	2.0	1	0.8	8	1.7	1	0.2

[a] Extrapyramidal syndrome included: slow initiation of motor activity, balance, gait and posture, lack of facial expression.

phrenia, baseline CGI and BPRS scales and time from onset ($\chi^2=11.71$, $P<0.001$). Mean change in baseline to endpoint CGI and BPRS scores were significantly higher in OG compared to CG (Table 6). PGI score was significantly lower in the OG compared to the control group ($P<0.001$) while mean change in the NOSIE scale was similar between both groups.

Efficacy was tested at several improvement levels in BPRS rating score: 390 patients (82%) in the OG against 320 (76.9%) in the CG showed a ≥40% reduction in the BPRS total scale ($P=0.040$). This result was confirmed with data obtained at the 60% reduction level ($P=0.001$), and those of the 80% level, too ($P=0.001$) (Fig. 1).

Median time (±S.D.) to discharge from hospital was similar for both groups (OG 21.4±12.9 vs. CG 21.8±13.8).

4. Discussion

This study is the largest prospective observational study conducted with atypical antipsychotics in the hospital

Table 6
Mean change in the CGI, PGI, BPRS and NOSIE scales by treatment group

	Olanzapine $N=483$	Control group $N=421$	Statistics	*P*-value
CGI[a]			ANCOVA	
Mean decrease (S.D.)	1.74 (1.11)	1.65 (1.08)		
	1.8 (1.11)[a]	1.6 (1.08)[a]	$F=8.79$	0.0031
BPRS total[a]			ANCOVA	
Mean decrease (S.D.)	26.8 (14)	25.5 (14.5)		
	27.6 (14)[a]	24.8 (14.5)[a]	$F=12.61$	<0.001
BPRS positive[a]			ANCOVA	
Mean decrease (S.D.)	8.7 (5.1)	8.7 (5.3)		
	9.1 (5.1)[a]	8.4(5.3)[a]	$F=5.68$	0.017
BPRS negative[a]			ANCOVA	
Mean decrease (S.D.)	3.4 (3.3)	2.5 (3.5)		
	3.4 (3.3)[a]	2.6(3.5)[a]	$F=18.03$	<0.0014
BPRS agitation[b]			ANCOVA	
Mean decrease (S.D.)	9.9 (6.4)	9.9 (6.6)	$F=12.06$	0.0005
	10.3 (6.4)[b]	9.3 (6.6)[b]		
BPRS depression 2			Wilcoxon	
Mean decrease (S.D.)	1.5 (2.1)	1.1 (1.9)	$Z=-2.89$	0.0039
NOSIE			Wilcoxon	
Mean change (S.D.)	19.72 (14.05)	19.79 (16.91)	$Z=-0.68$	0.4932
PGI			Wilcoxon	
Mean change (S.D.)	2.25 (0.91)	2.49 (0.88)	$Z=4.74$	<0.001

[a] Mean value adjusted for schizophrenia type, baseline value and duration length.
[b] Mean value adjusted for baseline value.

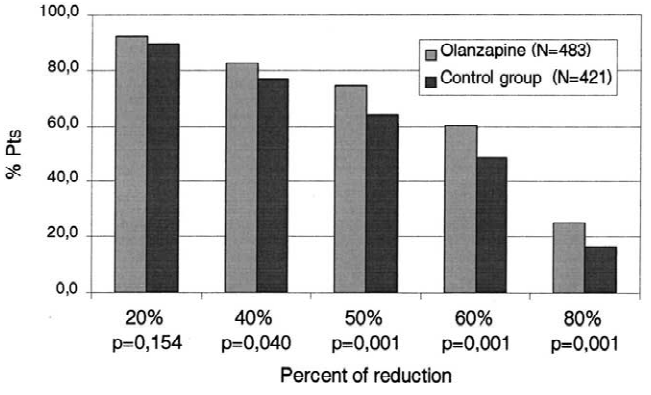

Fig. 1. BPRS rating scores levels of improvements: measurements of efficacy.

setting of which we are aware. It is subject to certain limitations which are inherent to large observational studies: (1) selection bias secondary to lack of randomisation, (2) additional problems in establishing unequivocal causal relationship, due to a heterogeneous control group and frequent use of concomitant medication, and (3) probable underreporting of adverse events compared to clinical trials. Acknowledging these limitations, the naturalistic design allows for the collection of information on what is really happening in the clinical setting without the artefacts of an experimental intervention.

The primary objective was to evaluate the safety and effectiveness of olanzapine in its routine use compared to routine clinical practice with conventional antipsychotic drugs. The study has the advantage of including a control group, in contrast to other observational studies with antipsychotics published recently (Chouinard et al., 1998; Gutierrez et al., 1998). The number of patients included in this study is particularly noteworthy, as it makes this particular study the largest prospective observational analysis with antipsychotic drugs of which we are aware in the hospital setting. The retention rate for our study has also been very high (approximately 87%) in comparison with controlled clinical trials.

The mean dose of olanzapine is higher compared to that reported in an observational study in schizophrenic patients in the out-patient setting, conducted in Spain in 1998 (Gómez et al., 2000). Mean olanzapine dose in this study was 13.01 mg/day, versus initial and final doses of 14.4 and 17.7 mg/day, respectively, in the present study. Similarly, mean haloperidol dose in the out-patient study was 13.6 versus 15.4 and 15.3 mg/day in this in-patient study. The doses of haloperidol used by Spanish doctors in this study may be regarded as quite high, nevertheless, we think it reflects properly the treatment of schizophrenia in routine clinical practice in Europe. Additionally, it should be considered that patients included in this study were treated in acute psychiatric settings and the need for rapid control of agitation and severe psychotic symptoms is crucial. In a study that addressed this issue (Van Putten et al., 1990), the authors compared the efficacy of different doses of haloperidol (5, 10 and 20 mg/day) in an open study involving acute schizophrenic patients (patients with a history of lack of response to neuroleptic treatment were excluded). Although the usefulness of 20 mg/day was not superior to lower doses, in patients who maintained this dose, the clinical response was obtained much more rapidly in the first 2 weeks than in patients receiving 5 and 10 mg/day (68% of response rate vs. 6 and 33%, respectively).

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.

There are few reasons for using a combination of antipsychotics in the treatment of schizophrenia, but apparently it is an extended practice in Spain, but the tendency is to use olanzapine less frequently in combination than conventional antipsychotics. The rate of combination of olanzapine with conventional antipsychotics did not increase during the study, which suggests that the addition of a conventional drug is not a way to increase efficacy in patients who do not respond well initially, but a treatment pattern that is decided a priori.

There was a small proportion of patients who switched treatment during the study. This is a confirmation that clinicians tend to avoid treatment changes during acute hospital stay. Up to 96.5% of patients in OG and 91.2% in CG did not switch therapies during their hospital stay, suggesting that the oral drug on which the patient is initiated, upon admission, will most likely be the drug prescribed at endpoint. It is particularly noteworthy that no patients discontinued olanzapine to start treatment with conventional drugs due to side effects.

4.1. 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 most expected adverse events in olanzapine treatment, according to European SPC are somnolence and weight gain. Somnolence was reported in 3.3% of cases in OG, and in 2.9% in the CG. These are very low figures for both groups, particularly taking into account that around 60% of the patients in both groups received benzodiazepines. It is likely that somnolence and sedation are seen as

therapeutic in this patient population and not reported as an adverse event. Incidence of reported weight gain was higher in OG compared to CG (1.7 vs. 0.2%) but low in both groups. In this study, there was no systematic collection of weight and participating clinicians reported weight changes as adverse events when deemed appropriate. It may have led to underreporting of weight gain. Nevertheless, we should take into account that a short-term study conducted in the in-patient setting, where diet may be controlled is not relevant to evaluate the weight change liability of antipsychotic drugs.

The incidence of extrapyramidal symptoms was significantly lower in the olanzapine group, compared to the control group ($P=0.001$). The incidence of specific EPS (dystonia, hypertonia, hypokinesia, tremor, akathisia and dyskinesia) with olanzapine was also significantly lower ($P\leq0.001$) compared to conventional antipsychotics, and the incidence in the subgroup treated with olanzapine monotherapy was even lower. In the interpretation of the figures for the control group we should take into account that 59% of the patients were receiving concomitant anticholinergics from the beginning of the study. These results confirm the results of controlled clinical trials where olanzapine has been shown to have a lower incidence of extrapyramidal symptoms in comparison with haloperidol (Tollefson et al., 1997). The present study confirms this lower incidence of extrapyramidal symptoms in routine clinical practice in the hospital setting where use of high doses and combination with conventional antipsychotics take place.

The rates of EPS reported in the olanzapine group are similar to the rates reported in a placebo and haloperidol-controlled clinical trial in a similar patient population. Rates of EPS in the control group are similar to the rates reported for haloperidol in that trial (Beasley et al., 1996b).

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 optimal in terms of the efficacy/tolerability ratio.

The incidence of anticholinergic effects (dry mouth, constipation, diplopia, urinary retention, difficulties in concentration, and confusion) were low in both groups, and similar in magnitude. Excluding from both groups those patients taking anticholinergic medication (15% in OG and 59% in CG), the incidences are even smaller and still similar for both groups. This confirms that olanzapine, despite having a high in vitro affinity with muscarinic receptors, presents in vivo, a slight anticholinergic activity (Bymaster et al., 1999).

4.2. Effectiveness

The improvement in clinical status as measured by changes in CGI and the BPRS (total scores and positive, negative, agitation and depression sub scores) was significantly greater in OG compared to CG, when adjusting for relevant baseline variables. There were no significant differences in the NOSIE scale.

For interpreting these results, we should take into account several factors. Although effectiveness analysis had been conducted, those analyses should be seen as exploratory since this study was not designed to investigate specifically this issue. There were significant differences at baseline in most of the clinical evaluations (CGI, BPRS total, positive and agitation subscores, and NOSIE). Adjustments have been performed in relevant variables where baseline differences have been found. Obviously the study was not randomised and it is not surprising that the samples presented small differences in their baseline severity. These findings suggest that clinicians at the time of the study were slightly more likely to treat severe psychotic patients with conventional antipsychotics rather than with olanzapine. It may be related to the fact that patients treated with IM antipsychotics upon admission, will tend to remain on the same drug in the oral phase (14.8% of olanzapine-treated patients received prior IM medication compared to 22.8% in the control group). Nevertheless, it is unclear to what extent these baseline differences may have biased the results in favour of olanzapine. On the contrary, the higher the baseline values are, the greater improvement may be shown. In fact, we have confirmed in our database that those patients with greater baseline BPRS scores had a greater proportional decrease in BPRS.

They were different in age and duration of illness, but not in gender and schizophrenia subtype. The number of previous hospital admissions, the total time spent in hospital during the past year and the duration of previous admission may, in fact, be better estimations of potential treatment-refractoriness. These variables were not different across treatment groups.

A previous clinical trial in acute hospitalised patients with schizophrenia, showed similar efficacy for olanzapine and haloperidol (Beasley et al., 1996b). Nevertheless, the highest olanzapine dose arm tested in this trial (15 mg/day) showed greater improvement compared to haloperidol on some efficacy measures. Our results point in the direction that, at the doses used in this study, effectiveness of olanzapine in acute patients may in fact be greater compared to conventional antipsychotics. Nevertheless, baseline differences in severity may limit the comparability of the study groups.

In summary, olanzapine has been shown to be well tolerated and appears to be effective in a large unselected sample of acutely psychotic schizophrenic in-patients. Olanzapine was better tolerated in terms of EPS compared to treatment with conventional antipsychotics. The effectiveness of olanzapine treatment in routine clinical prac-

tice, may in fact be greater than the effectiveness of conventional antipsychotics.

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