International Clinical Psychopharmacology 2002, **17**:287–295

Treatment of severely psychotic inpatients with schizophrenia: olanzapine versus other antipsychotic drugs

J.L. Carrasco[a], M. Gutiérrez[b], J.C. Gómez[c], R. Escobar[c], E. Álvarez[d], F. Cañas[e], J. Bobes[f], J. Gascón[g] and J. Gibert[h]

[a]*Fundación Jiménez Díaz, Madrid,* [b]*Hospital de Cruces, Baracaldo,* [c]*Eli Lilly and Company, Madrid,* [d]*Hospital de la Santa Cruz y San Pablo, Barcelona,* [e]*Hospital Psiquiátrico de Madrid,* [f]*Universidad de Oviedo, Oviedo,* [g]*Hospital Mutua de Tarrasa, Barcelona and* [h]*Universidad de Cádiz, Cádiz, Spain*

Correspondence to Rodrigo Escobar, Avda. de la Industria, 30, 28108 Alcobendas, Madrid, Spain
Tel: +91 663 5000; fax: +91 663 5231; e-mail: escobar_rodrigo@lilly.com

Received: 11 January 2001; accepted 4 September 2002

Nine hundred and ten schizophrenic inpatients suffering from acute psychotic episodes were included in a naturalistic study. Patients were prescribed treatment with olanzapine (OLZ) or with typical antipsychotic (TYP) drugs. Patients receiving another atypical antipsychotic were excluded. Of the whole sample, 483 (53.4%) were treated with olanzapine and 421 (46.6%) with typical antipsychotics. Three specific subpopulations of greater severity were defined: patients with prominent psychotic symptoms, agitated patients, and patients initially treated with intramuscular (i.m.) medication because of their acute clinical condition. Severity of illness was assessed using the Clinical Global Impression (CGI) scale for severity, the Brief Psychiatric Rating Scale (BPRS) and the Nursing Observational Scale for Inpatient Evaluation. Baseline differences were adjusted per data analysis. The mean change from baseline to endpoint of overall symptomatology (total BPRS score) was significantly greater in the olanzapine group compared to the typical antipsychotic-treated group, both in the sample of patients with prominent positive symptoms ($P < 0.001$) and in the sample of agitated patients ($P = 0.015$). Significant differences were also found in BPRS positive scores, BPRS negative scores and CGI scores in these two populations. Patients who had received previous i.m. drugs showed no statistically significant differences in symptomatic improvement between both treatments groups, except for a more favourable response of BPRS negative subscores in the olanzapine group ($P = 0.015$). The results suggest that olanzapine may be considered as a first line treatment for severely psychotic inpatients with schizophrenia. Int Clin Psychopharmacol 17:287–295 © 2002 Lippincott Williams & Wilkins

Keywords: schizophrenia, olanzapine, inpatients, severe psychotic, antipsychotics

INTRODUCTION

Schizophrenia is a complex psychotic disorder, affecting approximately 1% of the world population, and has a great impact on patient functioning due to clinical manifestations diminishing the ability of subjects to adapt to their environment. Positive symptoms lead to an interruption in coherent thinking anxiety, and difficulty in carrying out daily activities. Negative symptoms have a significant impact on social functioning, resulting in loneliness and isolation (Breier, 2001). Concomitant affective symptoms have been inversely related to schizophrenic patients' quality of life (Tollefson and Andersen, 1999). The suicide rate in people suffering from this disease is approximately 10% (Breier and Astracham, 1984) and has been identified as a specific cause for the increased number of deaths in schizophrenic men (Osby *et al*., 2000). The cognitive deficit associated with schizophrenia has also been related to poor social and occupational adaptation (Green, 1996; Brekke *et al*., 1997).

Most patients present for hospital admission during the acute phase of illness, resulting from either a relapse of a previously stable condition, or within the

context of a first episode of the disease. The acute phase is often characterized by agitation, hostility and an increase in positive symptoms. Conventional antipsychotic drugs have been routinely used for treatment of acute schizophrenic patients. Despite the fact that these drugs are effective in addressing positive symptoms, their efficacy in treating negative, depressive and cognitive symptoms is generally very limited or non-existent. Furthermore, conventional antipsychotics have been related to a high rate of side-effects (Medalia *et al*., 1988; Cassens *et al*., 1990; Gerlach, 1991), such as extrapyramidal symptoms, including highly unpleasant and painful ones such as acute dystonia (Addonizio and Alexopoulos, 1988).

Atypical antipsychotics have generally been found to be more effective than conventional antipsychotics against negative symptoms (Collaborative Working Group on Clinical Trial Evaluation, 1998). Olanzapine has demonstrated greater efficacy than haloperidol in a wide range of schizophrenic patients with positive, negative or mixed symptoms (Beasley *et al*., 1996; Beasley *et al*., 1997; Tollefson and Sanger, 1997; Gomez and Crawford, 2001).

However, some clinicians do not consider new antipsychotic drugs to be as effective as traditional ones in the treatment of acute exacerbations of the disease. Nonetheless, an improvement in agitation in schizophrenics has recently been reported with these new antipsychotic drugs (Kinon *et al*., 2001), thereby reflecting their usefulness in more severely affected patients.

Conversely, clinical studies frequently fail to include the typical patients seen in everyday psychiatric practice. This is especially true for diseases such as schizophrenia, where the type of patients seen on a daily basis by clinicians have limited insight, may abuse substances and present some concomitant illness, and may therefore be very different from those typically enrolled in clinical trials.

Severe psychotic patients may not be good candidates for experimental studies, but may well be included in non-experimental observational studies. The main objective of this study (EUROPA study) was the assessment of the safety of olanzapine (particularly the presence of extrapyramidal symptoms) and its effectiveness in a cohort of acute schizophrenic inpatients admitted to psychiatric units and treated under normal conditions versus another cohort, who were treated with conventional antipsychotic drugs (Alvarez *et al*., 2001). The purpose of the current subanalysis was to evaluate the effectiveness of olanzapine compared to conventional neuroleptics in the treatment of patients with a greater severity of illness.

METHODS

Subjects

Nine hundred and ten schizophrenic patients (F20 of the ICD-10, World Health Organization), hospitalized for an acute psychotic episode, were studied. Patients were admitted to 83 psychiatric units from January 1999 to September 1999 in a naturalistic fashion. Thus, all patients receiving treatment with olanzapine or with a typical antipsychotic drug as their main medication were included in the study. Patients receiving an atypical antipsychotic other than olanzapine (clozapine, risperidone, quetiapine or sertindole) were excluded. Although informed consent was not required for observational studies in Spain, when the study was undertaken, patients were fully informed as to the aim of the study and oral consent to participate was obtained prior to enrolment. They were advised that they could withdraw at any time during the course of the study and confidentiality was guaranteed as no details were registered in the study documentation.

Study protocol

At every centre, investigators were asked to include six patients in both treatment groups to reduce selection bias, although it was the investigators' responsibility to assign patients to the different groups: the olanzapine-treatment group (OLZ) or to the typical antipsychotic-treatment group (TYP), in which patients received one or more typical antipsychotic medications as core treatment. In the OLZ, patients might receive olanzapine alone or in combination with additional doses of a typical antipsychotic drug if clinicians prescribed them for clinical reasons. The use of intramuscular (i.m.) antipsychotic drugs at admission, prior to initiation of oral treatment, was not considered an exclusion criterion for the purpose of this study.

Severity of illness was assessed at baseline with the Clinical Global Impression-Severity scale (CGI-S, items rated 1–7), and the Brief Psychiatric Rating Scale (BPRS, items rated 0–6). Behavioural variables were also assessed using the Nursing Observational Scale for Inpatient Evaluation (NOSIE). Extrapyramidal symptoms were appraised using a specific questionnaire based on the extrapyramidal symptom section of the UKU scale (dystonia, hypertonia, hypokinesia, tremor, dyskinesia and akathisia).

The initial hypothesis was that olanzapine was not as effective as typical antipsychotics in patients with greater severity of illness. We therefore compared the outcome of inpatients with a greater severity of illness when treated with olanzapine versus a cohort of patients with similar severity of illness treated with typical antipsychotics. Therefore, three specific sub-

populations of the whole sample were defined *a priori* in this study which were characterized as having greater disease severity: (i) Patients with Prominent Psychosis Symptoms (PPS) (conceptual disorganization, hallucinatory behaviour, unusual thought content, and suspiciousness) were considered to be those with a baseline score ≥ 12 (50% of the maximum score) on those items of BPRS; (ii) agitated patients, defined as those participants with a baseline score > 15 (50% of the maximum score) on the cluster of agitation items of the BPRS (anxiety, tension, uncooperativeness, hostility, and excitement; and (iii) i.m. medication, patients who were initially treated with i.m. medications because of their acute clinical condition. The three specific subpopulations were compared. The three *a priori* defined groups were not exclusive (i.e. patients could belong to more than one group).

During the study, any dose adjustments for clinical reasons were allowed. Should a lack of efficacy, adverse effects or other reasons arise, patients could be switched from one group to another, as the investigator deemed best.

Efficacy and safety ratings

Treatment efficacy was measured as the change in symptomatic scale scores and on the CGI. Responders were defined as patients with a 40% reduction in BPRS scores from baseline, a final BPRS score < 18, or CGI ≤ 3.

Statistical analysis

The Biometrics Department of Phoenix International carried out the statistical analyses. The data were entered into two simultaneous databases by different individuals and later contrasted to eliminate errors. An SAS statistical software package (SAS version 6.12 for Windows; SAS Institute Inc., Cary, NC, USA) was used for verification, validation and data analysis.

The analyses were carried out on the basis of 'intention to treat'; six patients were excluded from the analysis: five took medication that was banned and one had no treatment group defined.

Statistical analyses were performed, following the LOCF approach, for all time-points except in those cases in which patients switched from one group to the other. Data for patients who were switched from olanzapine to a conventional antipsychotic, or data for patients who switched from conventional antipsychotic to olanzapine were analysed up until the point at which medication was switched.

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. Quantitative variables are described using means, medians, SDs and ranges. Discrete variables are described by means of frequencies and percentages. For the statistical analyses of continuous variables, parametric and non-parametric tests were used depending on applicability constraints (normality and variance homogeneity) and the nature of the variable. For comparisons of age and number of years since the onset of the illness, a Wilcoxon test was used. Mean changes in the CGI, BPRS and NOSIE scales were analysed by means of either an ANCOVA or ANOVA test, when applicable. Adverse events are presented by number and percentage; the number of extrapyramidal symptoms was compared using chi-squared or Fisher's exact test. To analyse 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's exact test were used. A two-tailed $P < 0.05$ was considered statistically significant for all tests. Adjustments were performed for relevant variables to take baseline differences into account.

RESULTS

Global results of the study have been reported in preliminary form elsewhere (Alvarez *et al.*, 2001). From the whole sample, 483 (53.4%) patients were treated with olanzapine [receiving olanzapine as monotherapy ($n = 355$) or in combination with another antipsychotic ($n = 128$)]. No significant differences were found between these groups in terms of demographic baseline data, BPRS total, BPRS positive and negative, and NOSIE, or with respect to mean changes in BPRS total, BPRS positive and negative, CGI and NOSIE. Differences were found in baseline CGI (olanzapine alone, mean 5.0, SD 0.81; olanzapine in combination with another antipsychotic, mean 5.23, SD 0.85; $P = 0.0081$) and treatment emergent extrapyramidal symptoms (olanzapine alone, 14.1%; olanzapine in combination with another antipsychotic, 24.2%; chi-squared $= 6.82$; $P = 0.009$). The TYP group (typical antipsychotic used as the main treatment either alone or in combination) included 421 (46.6%) patients. No significant differences in clinical characteristics were observed between the OLZ group and TYP group at baseline, except for mean age [olanzapine, 35.3 years versus typical antipsychotic, 37.0 years ($P = 0.016$) and length of illness, both of which were greater in the TYP group than in the OLZ group (10.6 years versus 12.9 years ($P > 0.001$)], the differences were small in absolute terms (Table 1).

Table 1. Demographic and clinical characteristics of the overall sample at baseline

Characteristics	Olanzapine ($n = 483$)	Control group ($n = 421$)	Statistics	*P*-value
Age (years)				
Mean (SD)	35.3 (11.1)	37.0 (11.4)	Wilcoxon, $Z = 2.416$	0.016
Median	33	35		
Range	16–74	17–76		
Gender (% males)	67.2	66.5	Chi-squared = 0.04	0.838
Time from onset (years)				
Mean (SD)	10.6 (9.3)	12.9 (9.7)	Wilcoxon, $Z = 3.947$	< 0.001
Median	9	12		
Schizophrenia subtype (%)			Chi-squared = 2.69	0.694[a]
Paranoid	71.0	75.0		
Undifferentiated	12.5	9.3		
Residual	7.1	6.7		
Disorganized	8.5	8.3		
Catatonic	0.8	0.7		
No. of previous hospitalizations				
Mean (SD)	4.1 (6.4)	4.3 (6.1)	Wilcoxon, $Z = 0.390$	0.694
Median	3	3		

[a]Overall *P*-value.

Table 2. Baseline scores of severe psychotic population

Characteristics	PPS population		Agitated patient population		i.m. Medication population	
	OLZ ($n = 352$)	TYP ($n = 342$)	OLZ ($n = 219$)	TYP ($n = 229$)	OLZ ($n = 68$)	TYP ($n = 96$)
Baseline CGI score						
Mean (SD)	5.2 (0.8)	5.4 (0.8)	5.2 (0.8)	5.4 (0.8)	5.2 (0.9)	5.3 (0.7)
Wilcoxon	$P = 0.002$		$P = 0.003$		$P = 0.539$	
Baseline BPRS total						
Mean (SD)	47.0 (10.9)	49.0 (11.5)	51.1 (10.4)	52.8 (10.8)	45.4 (12.6)	47.3 (12.1)
ANOVA	$P = 0.019$		$P = 0.086$		$P = 0.322$	
Baseline BPRS positive						
Mean (SD)	16.2 (2.9)	16.9 (3.2)	15.6 (3.9)	16.8 (4.1)	14.7 (4.3)	16 (4.1)
ANOVA	$P = 0.002$		$P = 0.003$		$P = 0.052$	
Baseline BPRS negative						
Mean (SD)	7.5 (3.9)	7.4 (4.3)	7.1 (4.1)	7.1 (4.3)	7.3 (4.3)	6.4 (4.1)
ANOVA	$P = 0.824$		$P = 0.846$		$P = 0.156$	
Baseline BPRS agitation						
Mean (SD)			19.5 (3.5)	19.8 (3.5)	15.5 (6.6)	17 (6.2)
ANOVA	–		$P = 0.312$		$P = 0.157$	
Baseline NOSIE						
Mean (SD)	47.0 (15.1)	51.0 (16.9)	51.8 (14.5)	55.0 (16.3)	46.4 (17.6)	51.1 (17.5)
ANOVA	$P = 0.002$		$P = 0.047$		$P = 0.133$	
Baseline EPS						
(%)	37.5	33.6	34.7	30.1	55.9	31.3
Chi-squared	$P = 0.287$		$P = 0.301$		$P = 0.002$	

PPS, Prominent Psychotic Symptoms; i.m., intramuscular; OLZ, olanzapine; TYP, typical antipsychotic.

Three hundred and fifty-two patients (73%) belonging to the olanzapine group had severe positive symptoms as the prominent clinical feature versus 342 patients (81.2%) in the typical antipsychotic-treated group. Severity at baseline as measured by the BPRS total and positive subscore, CGI-S and NOSIE was slightly greater in the TYP group of patients. BPRS negative subscores were similar in both groups (Table 2).

Two hundred and nineteen patients in the OLZ group (45.3%) qualified for prominent agitation features, as compared to 229 patients (54.4%) in the TYP group. No differences were observed between both groups of patients at baseline with respect to the BPRS total, negative and agitation subscore rating. However, BPRS positive scores, CGI and NOSIE scores were higher in the group subsequently treated with typical antipsychotics (Table 2).

One hundred and sixty-four patients (18.1% of the entire sample) received i.m. antipsychotic medication at admission as needed for behavioural or symptomatic severity. Sixty-eight patients (41.5%) of these patients were assigned to the olanzapine-treatment group and 96 (58.5%) went on to be treated with typical antipsychotics. Haloperidol was the most commonly prescribed i.m. drug (76%) at admission. No differences were found in terms of baseline CGI, BPRS total, positive, negative and agitation subscale scores and NOSIE between the patients included in the OLZ group and those in the TYP group (Table 2).

In the group of patients treated with i.m. medication at admission, baseline EPS (extrapyramidal symptoms) were more frequent among those who were assigned to treatment with olanzapine compared to those who were assigned to treatment with typical antipsychotics (55.9% versus 31.3%, respectively; $P = 0.002$) (Table 2).

This baseline difference was subsequently corrected during the treatment trial, since worsening of previous EPS, treatment emergent EPS (TEAE, Treatment Emergent Adverse Event) or general adverse effects were significantly associated with the TYP patient group compared to the OLZ patient group ($P = 0.001$). This difference was observed either in the whole sample or in the different subsamples of i.m.-treated patients, prominent positive symptoms, or agitated patients (Table 3).

Adverse events other than EPS presented more frequently during treatment with typical antipsychotics than with olanzapine (55.6% versus 27.3%, chi-squared = 75.71, $P = 0.001$). Table 3 presents a list of adverse events classified and coded according to the COSTART dictionary that were present in at least two patients during the study. No cases of leukopenia were reported throughout the study. One patient in the PPS population and included in the OLZ group with a prior history of untreated chronic obstructive lung disease and atrial flutter died as a result of acute respiratory depression related to respiratory infection. The treating physician considered that the event was unrelated to the study drug.

The mean change from baseline to endpoint of overall symptoms (BPRS total) is shown in Table 4. This change was significantly greater in the OLZ group compared to the TYP group, both in the sample of patients with prominent positive symptoms ($P < 0.001$), following adjustment of values to account for baseline differences, and in the sample of agitated patients ($P = 0.015$). Significantly greater improvements with olanzapine versus typical antipsychotics were also found in BPRS positive scores, BPRS negative scores and CGI scores in these two populations. The NOSIE scale scores did not show significant differences between groups (Table 4). In the agitated population group, the mean decrease in the BPRS agitation subscale was significantly greater ($P = 0.035$) in the OLZ patient group (mean 14.5, SD 5.3) than in the TYP patient group (mean 13.4, SD 6.1).

The analysis of patients who had received previous i.m. drugs showed no statistically significant differences in symptomatic improvement between treatments groups, except for a more favourable response of BPRS negative subscores in the olanzapine group ($P = 0.015$) (Table 4).

Mean duration of hospitalization was similar for both treatment groups (OLZ, 21.4 ± 12.9 days versus TYP, 21.8 ± 13.8 days) in the overall population. Doses of olanzapine and haloperidol throughout the study in the different subpopulations are shown in Table 5, Haloperidol was prescribed for 76% of the PPS population, 74% of the Agitated Population and for 76% of patients receiving i.m. medication. Other conventional antipsychotics used include chlorpromazine, clotiapine, sulpiride, fluphenazine, levopromazine, perphenazine, pimozide, thioproperazine, thioridazine, trifluoperazine, zuclopenthixol and droperidol.

DISCUSSION

Most antipsychotics have been shown to be effective in the treatment of schizophrenia by reducing the severity of symptoms and improving the behavioural control of patients. Nonetheless, clinicians still tend to consider classic neuroleptics as more beneficial in treating acute schizophrenic patients with agitated behaviour or severe symptoms. In fact, this non-randomized, naturalistic study demonstrates this tendency of clinicians to assign patients who had previously received i.m. medication or with agitated symptoms to the typical antipsychotic group. It is possible that this idea has been supported by the current inability to administer atypical antipsychotic drugs intramuscularly, thereby making i.m. typical antipsychotics the first treatment for acute illness, followed by the oral form of the same agent. However, controlled trials with atypical antipsychotics failed to demonstrate that they were less effective than haloperidol in the control of psychotic symptoms; there is even evidence originating from a large, international, double-blind, randomized clinical trial that olanzapine-treated patients experienced greater improvement compared to haloperidol-treated patients assessed during the acute phase (6 weeks) and maintenance phase (46 weeks) (Hamilton *et al*., 2000). Additionally there is evidence that i.m. olanzapine

Table 3. Treatment-emergent adverse events (TEAE) according to the COSTART dictionary

	Overall population		PPS population		Agitated population		i.m. Medication	
65	OLZ ($n = 483$)	TYP ($n = 421$)	OLZ ($n = 352$)	TYP ($n = 342$)	OLZ ($n = 219$)	TYP ($n = 229$)	OLZ ($n = 68$)	TYP ($n = 96$)
EPS, *n* (%)	91 (18.8) Chi-squared, $P = 0.001$	205 (48.7)	61 (17.3)	160 (46.9)	41 (18.7) Chi-squared, $P = 0.001$	103 (45.2)	13 (19.1) Chi-squared, $P = 0.001$	45 (46.9)
TEAE, *n* (%)	132 (27.3) Chi-squared, $P = 0.001$	234 (55.6)	99 (28.1)	197 (57.6)	64 (29.2) Chi-squared, $P = 0.001$	126 (55.0)	21 (30.9) Chi-squared, $P = 0.010$	49 (51.0)
Abnormal vision	1 (0.2)	5 (1.2)	1 (0.3)	4(1.2)	1 (0.5)	1 (0.4)	0 (0)	1 (1.0)
Akathisia	22 (4.6)	75 (17.8)	11 (3.1)	61 (17.8)	11 (5.0)	44 (19.2)	3 (4.4)	16 (16.7)
Akinesia	2 (0.4)	6 (1.4)	0 (0)	4 (1.2)	0. (0)	0. (0)	0 (0)	3 (3.1)
Anxiety	8 (1.7)	7 (1.7)	7 (2.0)	6 (1.8)	5 (2.3)	5 (2.2)	0 (0)	1 (1.0)
Asthenia	15 (3.1)	22 (5.2)	12 (3.4)	20 (5.8)	10 (4.6)	13 (5.7)	3 (4.4)	7 (7.3)
Constipation	5 (1.0)	8 (1.9)	3 (0.9)	8 (2.3)	3 (1.4)	6 (2.6)	1 (1.5)	2 (2.1)
Dry mouth	12 (2.5)	16 (3.8)	9 (2.6)	14 (4.1)	5 (2.3)	9 (3.9)	1 (1.5)	4 (4.2)
Dysarthria	2 (0.4)	8 (1.9)	1 (0.3)	6 (1.8)	2 (0.9)	3 (1.4)	1 (1.5)	1 (1.0)
Dyskinesia	5 (1.0)	10 (2.4)	4 (1.1)	9 (2.6)	3 (1.4)	6 (2.6)	1 (1.5)	2 (2.1)
Dystonia	8 (1.7)	43 (10.2)	7 (2.0)	38 (11.1)	3 (1.4)	25 (10.9)	2 (2.9)	10 (10.4)
Extrapyramidal symptoms	4 (0.8)	16 (3.8)	2 (0.6)	14 (4.1)	3 (1.4)	9 (3.9)	1 (1.5)	2 (2.1)
Hypertonia	27 (5.6)	81 (19.2)	22 (6.3)	70 (20.5)	14 (6.4)	47 (20.5)	4 (5.9)	17 (17.7)
Hypokinesia	44 (9.1)	92 (21.9)	34 (9.7)	75 (21.9)	21 (9.6)	45 (19.7)	8 (11.8)	20 (20.8)
Hypotension	2 (0.4)	4 (1.0)	1 (0.3)	4 (1.2)	0. (0)	1 (0.4)	1 (1.5)	0 (0)
Increased salivation	1 (0.2)	8 (1.9)	0 (0)	5 (1.5)	0. (0)	3 (1.4)	0 (0)	0 (0)
Insomnia	5 (1.0)	4 (1.0)	2 (0.6)	4 (1.2)	3 (1.4)	2 (0.9)	1 (1.5)	1 (1.0)
Nervousness	3 (0.6)	6 (1.4)	2 (0.6)	5 (1.5)	2 (0.9)	3 (1.4)	1 (1.5)	1 (1.0)
Somnolence	16 (3.3)	12 (2.9)	11 (3.1)	10 (2.9)	10 (4.6)	8 (3.5)	7 (10.3)	6 (6.3)
Tremor	32 (6.6)	98 (23.3)	26 (7.4)	88 (25.7)	13 (5.9)	52 (22.7)	4 (5.9)	28 (19.2)
Weight gain[a]	8 (1.7)	1 (0.2)	8 (2.3)	1 (0.3)	3 (1.4)	0. (0)	0 (0)	0 (0)

[a]Number of subjects who presented this adverse event. PPS, Prominent Psychotic Symptoms; i.m., intramuscular; OLZ, olanzapine; TYP, typical antipsychotic; EPS, extrapyramidal symptoms.

Table 4. Mean change in the Clinical Global Impression (CGI), Brief Psychiatric Rating Scale (BPRS), and Nursing Observational Scale for Inpatient Evaluation (NOSIE) scales by population

	PPS population		Agitated population		i.m. medication	
	OLZ ($n = 352$)	TYP ($n = 342$)	OLZ ($n = 219$)	TYP ($n = 229$)	OLZ ($n = 68$)	TYP ($n = 96$)
CGI[a]						
Mean decrease (SD)	1.9 (1.1) ANCOVA, $P = 0.001$	1.7 (1.1)	2 (1.1) ANCOVA, $P < 0.001$	1.8 (1.1)	1.9 (1.3) Wilcoxon, $P = 0.099$	1.6 (1.2)
BPRS total[b]						
Mean decrease (SD)	30.2 (14.0) ANCOVA, $P < 0.001$	27.0 (14.8)	34.2 (13.2) ANOVA, $P = 0.015$	30.9 (15)	30.1 (15.4) ANOVA, $P = 0.320$	27.5 (16.4)
BPRS positive[b]						
Mean decrease (SD)	10.3 (4.9) ANCOVA, $P = 0.011$	9.4 (5.2)	10.6 (4.9) ANCOVA, $P = 0.008$	9.5 (5.5)	9.5 (5.3) ANOVA, $P = 0.988$	9.5 (6.1)
BPRS negative						
Mean decrease (SD)	3.5 (3.3) ANOVA, $P = 0.002$	2.7 (3.7)	3.6 (3.5) ANOVA, $P < 0.001$	2.4 (3.8)	3.6 (3.5) ANOVA, $P = 0.015$	2.2 (3.8)
NOSIE[b]						
Mean change (SD)	21.3 (14.1) ANCOVA, $P = 0.288$	20.2 (17.5)	25.6 (14.7) ANCOVA, $P = 0.134$	23.5 (17.7)	17.7 (15.9) ANOVA, $P = 0.057$	23.7 (18.5)

[a]Mean value adjusted for baseline range of values. [b]Mean value adjusted for baseline value. PPS, Prominent Psychotic Symptoms; i.m., intramuscular; OLZ, olanzapine; TYP, typical antipsychotic.

Table 5. Initial and final dose of treatments by population

	PPS population		Agitated population		i.m. Medication	
	OLZ ($n = 352$)	HAL ($n = 260$)	OLZ ($n = 219$)	HAL ($n = 170$)	OLZ ($n = 68$)	HAL ($n = 73$)
Initial dose						
Mean (SD)	14.9 (6.2)	15.5 (8.7)	15.3 (6.2)	16.6 (9.5)	15.0 (6.5)	16.3 (9.6)
Median	15	15	15	15	10	15
Final dose						
Mean (SD)	18.2 (6.3)	15.7 (9.3)	18.8 (6.3)	16.1 (9.8)	18.4 (6.2)	16.3 (9.6)
Median	20	15	20	15	20	15

PPS, Prominent Psychotic Symptoms; i.m., intramuscular; OLZ, olanzapine; HAL, haloperidol.

reduces agitation more rapidly than i.m. haloperidol when treating acute agitation in schizophrenia (Wright *et al*., 2001). It is possible that the severest and most agitated patients may not be properly represented in clinical studies, since these patients tend to be difficult to recruit and are therefore excluded from trials.

The rationale for this naturalistic study was to avoid the exclusion of highly agitated patients not normally included in controlled trials, and to reproduce everyday clinical practice because, first of all, it would allow us to observe how clinicians chose to treat severe psychotic patients and, second, to evaluate therapeutic differences between several drug options. The results of clinical trials should be confirmed by means of effectiveness studies in routine clinical practice. The benefits provided by the use of new antipsychotic drugs for the treatment of this type of schizophrenic patient should be evaluated in the context of daily clinical practice in patients receiving these drugs under the conditions in which they are normally used (Gomez *et al*., 2000). Naturalistic studies can also help determine whether the drug doses used by clinicians differ from manufacturers' recommendations, which are based on information obtained in randomized clinical trials. Moreover, naturalistic studies may explain such discrepancies when they do arise (Sacristan *et al*., 2000). The multicentre design (including 83 psychiatric units) was aimed at avoiding bias related to the particular treatment tendencies of a smaller number of hospitals.

The improvements in scores were numerically similar and, in some cases, significantly superior for olanzapine in this study. Olanzapine also proved to be more effective than haloperidol in this sample of severely ill patients (patients having prominent psychotic symptoms and agitated patients) as rated with the CGI, BPRS total and BPRS positive and negative subscales. The mean decrease on the BPRS agitation subscale in the agitated population was significantly greater in the olanzapine-treated group than in the typical antipsychotic-treated group. The length of hospital stay was similar for patients treated with olanzapine and those treated with haloperidol and other classical antipsychotics. Treatment-emergent EPS were significantly less frequent with olanzapine in the overall, PPS, agitated and i.m.-treated populations. Baseline EPS were significantly greater in the olanzapine group than in the i.m. treated population, possibly reflecting clinicians' bias in choosing olanzapine treatment for patients with EPS due to prior i.m. treatment with antipsychotics at baseline (i.m. lorazepam was not available in Spain when the study was undertaken). The clinical importance of a given medication relies not only on its advantage in terms of efficacy, but the overall risk-benefit of the two regimens is even more important. Olanzapine has greater therapeutic benefits, while causing fewer EPS and other adverse events than typical antipsychotics in these populations of patients, as observed in this study.

The dosing regime that patients were prescribed revealed that psychiatrists initiated and finalised treatments with similar doses when using typical antipsychotics, but that they prescribed lower doses of olanzapine initially, and then increased them during the study period. Interestingly, in a recent case series of 57 patients who received olanzapine for rapid tranquillization of acute psychosis, those patients who received 20 mg or more of olanzapine at baseline could be successfully managed with a lower dose at the final visit, whereas those who received a dose of less than 20 mg within the first 4 h had to have their dose incremented before stabilization was achieved (Karagianis *et al*., 2001).

Due to the nature of this observational study, there was no randomization and some baseline differences existed. Nonetheless, the baseline score was included as a covariate to adjust post baseline values for the effect of these baseline differences, thereby accounting for bias. More severe patients were initially assigned to the typical antipsychotic group. We expected that patients with higher baseline scores would have the greatest reduction in score, but the results revealed the opposite. The mean decrease in CGI, BPRS total, BPRS positive and negative subscale scores was generally greater in the olanzapine-treated patients in the three defined subpopulations (with the exception of the BPRS positive items in patients initially treated with i.m. medication, in which case the decrease was equal).

Weight gain has been reported during treatment with many conventional agents and new atypical agents; in addition, factors such as low baseline body mass index and non-white race have been reported as predictive in acute (6 weeks) weight changes (Basson *et al*., 2001). Weight gain was reported in this study only as a treatment emergent adverse event and investigators did not systematically record weight, which may be a reflection of the small proportion of patients who presented this adverse event in both treatment populations. The short mean duration of hospital stay in both groups also influences results regarding weight changes.

The results of this naturalistic study do not support the view that typical antipsychotic drugs are better for severely psychotic schizophrenic patients. In fact, the results are consistent with previous reports of open treatment (Karagianis *et al*., 2001; Kinon *et al*., 2001), and suggest that oral olanzapine, when appropriate, may be considered as a first line treatment for severely psychotic inpatients with schizophrenia.

Acknowledgements

Participants in the EUROPA Study Group: J.A. Hernández, R. Cap de Pon, A. Sandoval, C. Ros, M.C. Sáez, F. Martínez, F. Gázquez, A. Martínez, A.A. Taleb, A. de la Rubia, A. Simón, A. González, M.A. García, J.L. Figuerido, E.D. Vega, J.P. Jiménez, A. Iglesias, A.J. Pellejero, S. Parada, A. Casas, J.M. Blanco, J. Civeira, J.C. Díaz del Valle, M. Serrano, M.I. Gómez del Cid, M.V. Ortega, M. Alba, E. Linares, M. Gómez, C. Azpeleta, A. González, M. García, M. Camus, R. Gil, P. Samada, A. de Dios, J.V. Pozo, M.R. Fernández, J.C. Carazo, R.M. Alameda, J.F. Guardia, M. Silvestre, P. Calderón, L. Elvira, C. Merino, R. Muñóz, L. Coy, M. Delgado, C. de Gregorio, A. Moro, J. Valle, P. Alcinari, S. Pérez, Z. Fernández, R. Gómez, F. Wamba, A. Sánchez, J.M. Bertolín, F. Moreno, D. Simón, M. Brito, C. Rodríguez, A. Trujillo, A. Higueras, P. Bustos, R. de Arce, L. Iglesias, M.P. Pérez, M. Torreblanca, J. García, M. Gulbaharian, P. Sopelana, M. Franco, J. Monforte, J. Sanahuja, M.E. Alea, J. Valle, P. Ramos, P. Nieves Ureña, M. Barceló, C. Ciscar, P.P. de la Fuente, J. Ribes, M. Camarero, J.V. Baeza, E. Navarro, E. López, T. Guilera, R. Calabuig, J. Morillas, Y. Zapico, J.M. Segovia, A. Díaz, L. Palicio, J.J. Madrigal, B. García, J. Fernández, J. Ferrer, E. Gómez, M.J. Montes, S. Escote, R. Coronas, G.

García, C. Antón, P. Moreno, C. Busuldo, J. Cobo, E. Miró, E. del Moral, J. Horta, A.M. Fargas, C. Martín Martín, J. Derecho, R. Iglesias, I. Querejeta, A. García, A.C. Sierra, E. García, I. Mateo, M.A. Caballero, G. Palenciano, F. Dourdill, D. Huertas, I. Tortajada, J. Pérez, J. Sanz, A. Redondo, J.C. González, F. Ballester, J. González, S. Sarro, C. Sarrí, J.M. Sánchez, L. Tifón, V. Vallés, L. Delgado, E. Hernández, M. Rodríguez, J. Lequerica, J. Pérez, L. Torremocha, L. Pérez, D. Arenas, J.L. Benavente, A. Robador, M.J. Luna, I. Zarranz, J.A. Sánchez, J. Casanova, P. Salgado, A. David Cabo, A. Paillissé, J.M. Jaquotot, R. Rodríguez, E. Pons, P. Alvarez, N. Casas, A. Yáñez, A. Rodríguez, E. Ibarrola, E. Basurto, J. Civeira, J.L. Figuerido, M.C. Sáez, F. Martínez, C. Merino, R. de Arce, P. Sopelana, J. Gómez, J.J. Madrigal, M.J. Montes, C. Busuldo. The study was supported by a grant from Eli Lilly and Company, Madrid (Spain).

REFERENCES

Addonizio G, Alexopoulos GS (1988) Drug-induced dystonia in young and elderly patients. *Am J Psychiatry* **145**:869–871.

Alvarez E, Gomez J, Sacristan JA, Bobes J, Cañas F, Carrasco JL, Gascón J (2001) Effectiveness and onset of action of olanzapine versus typical antipsychotic drugs in the treatment of inpatients with schizophrenia (EUROPA study). *Schizophr Res* **(Suppl)**:219.

Basson BR, Kinon BJ, Taylor CC, Szymanski KA, Gilmore JA, Tollefson GD (2001) Factors influencing acute weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. *J Clin Psychiatry* **62**:231–238.

Beasley CM Jr, Tollefson GD, Tran P, Satterlee W, Sanger T, Hamilton S (1996) Olanzapine versus placebo and haloperidol: acute phase results of the North American double-blind olanzapine trial. *Neuropsychopharmacology* **14**:111–123.

Beasley CM Jr, Hamilton SH, Crawford AM, Dellva MA, Tollefson GD, Tran PV, *et al*. (1997) Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. *Eur Neuropsychopharmacol* **7**:125–137.

Breier A, Astracham BM (1984) Characterization of schizophrenic patients who commit suicide. *Am J Psychiatry* **141**:206–209.

Breier A (2001) Introduction: a new era in the pharmacotherapy of psychotic disorders. *J Clin Psychiatry* **62(Suppl. 2)**:3–5.

Brekke JS, Raine A, Ansel M, Lencz T, Bird L (1997) Neuropsychological and psycho-physiological correlates of psychosocial functioning in schizophrenia. *Schizophr Bull* **23**:19–28.

Cassens G, Inglis AK, Appelbaum PS, Gutheil TG (1990) Neuroleptics: effects on neuropsychological function in chronic schizophrenic patients [review]. *Schizophr Bull* **16**:477–499.

Collaborative Working Group on Clinical Trial Evaluations (1998) Assessing the effects of atypical antipsychotics on negative symptoms [review]. *J Clin Psychiatry* **59(Suppl. 12)**:28–34.

Gerlach J (1991) New antipsychotics: classification, efficacy, and adverse effects [review]. *Schizophr Bull* **17**:289–309.

Gomez JC, Crawford AM (2001) Superior efficacy of olanzapine over haloperidol: analysis of patients with schizophrenia from a multicenter international trial. *J Clin Psychiatry* **62(Suppl. 2)**:6–11.

Gomez JC, Sacristan JA, Hernandez J, Breier A, Ruiz P, Antón C, Fontova E (2000) The safety of olanzapine compared with other antipsychotic drugs: results of an observational prospective study in patients with schizophrenia (EFESO study). *J Clin Psychiatry* **61**:335–343.

Green MF (1996) What are the functional consequences of neurocognitive deficits in schizophrenia? [review]. *Am J Psychiatry* **153**:321–330.

Hamilton SH, Edgell ET, Revicki DA, Breier A (2000) Functional outcomes in schizophrenia: a comparison of olanzapine and haloperidol in a European sample. *Int Clin Psychopharmacol* **15**:245–255.

Karagianis JL, Dawe IC, Thakur A, Begin S, Raskin J, Roychowdhury SM (2001) Rapid tranquilization with olanzapine in acute psychosis: a case series. *J Clin Psychiatry* **62(Suppl. 2)**:12–16.

Kinon BJ, Roychowdhury SM, Milton DR, Hill AL (2001) Effective resolution with olanzapine of acute presentation of behavioral agitation and positive psychotic symptoms in schizophrenia. *J Clin Psychiatry* **62(Suppl. 2)**:17–21.

Medalia A, Gold JM, Merriam A (1988) The effects of neuroleptics on neuropsychological test results of schizophrenics. *Arch Clin Neuropsychol* **3**:249–271.

Osby U, Correia N, Brandt L, Ekbom A, Sparen P (2000) Mortality and causes of death in schizophrenia in Stockholm county, Sweden. *Schizophr Res* **29**:21–28.

Sacristan JA, Gomez JC, Montejo AL, Vieta E, Gregor K, for the EFESO Study Group (2000) Doses of olanzapine, risperidone, and haloperidol used in clinical practice: results of a prospective pharmacoepidemiologic study. *Clin Therapeut* **22**:583–599.

Tollefson GD, Sanger TM (1997) Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. *Am J Psychiatry* **154**:466–474.

Tollefson GD, Andersen SW (1999) Should we consider mood disturbance in schizophrenia as an important determinant of quality of life? [review]. *J Clin Psychiatry* **60(Suppl. 5)**:23–30.

Wright P, Birkett M, David SR, Meehan K, Ferchland I, Alaka KJ, Saunders, *et al*. (2001) Double-blind, placebo-controlled comparison of intramuscular olanzapine and intramuscular haloperidol in the treatment of acute agitation in schizophrenia. *Am J Psychiatry* **158**: 1149–1151.