Study in the hospital setting: a multivariate analysis of a large naturalistic study in the hospital setting

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Objective: This study assessed the safety and effectiveness of the atypical antipsychotic olanzapine for the treatment of inpatients with acute schizophrenia. Furthermore, we evaluated patterns of use of olanzapine and their relationship to safety and effectiveness.

Patients and Methods: This was a prospective, comparative, randomized, open-label, observational study of 848 patients with schizophrenia (International Classification of Diseases, 10th edition) hospitalized due to an acute psychotic episode. Data were collected during patients' entire hospital stay. Safety of antipsychotic therapy was assessed with an extrapyramidal symptoms questionnaire (based on the UWA-Klinische Untersuchungsskala) and the report of spontaneous adverse events. Clinical status was assessed with the Brief Psychiatric Rating Scale (BPRS) and the Clinical Global Impressions-Severity of Illness (CGI-S). A multivariate statistical approach was employed.

Results: Patients treated with olanzapine in monotherapy had the lowest risk of developing extrapyramidal symptoms (11.2%), whereas patients treated with conventional antipsychotics had a higher risk (39.0%; p < 0.001). Patients treated with olanzapine in monotherapy (even patients with prominent positive symptoms) displayed a higher rate of response compared with conventional antipsychotics-treated patients (p = 0.007).

Conclusions: Olanzapine is a safe and effective treatment for patients with acute schizophrenia in the hospital setting, even for patients with prominent positive or agitation symptoms.

Key words: Safety, Effectiveness, Acute schizophrenia, Conventional antipsychotics, Olanzapine.

Schizophrenia is a major psychiatric disorder with an early age of onset, a chronic course, and a consequent adverse impact on patient's family, social, and occupational life. Antipsychotic drugs are used to treat acute psychotic episodes and reduce the risk of relapse. Since their introduction, these drugs have become the mainstay of treatment for schizophrenia, dramatically reducing the time patients spend in hospitals, thus allowing to shift the care to the community. However, relapse is still frequent among patients with schizophrenia and involves readmissions and long hospital stays, thereby consuming more resources. In addition to the personal and society costs, relapse in schizophrenia may be associated with clinical deterioration.

The most important factor that determines the possibility of symptom exacerbation and illness relapse is discontinuation of antipsychotic medication. Thus, treatment compliance constitutes a crucial issue in clinical practice to reduce both suffering of patients and the global costs of the disorder to the society. Poor adherence to treatment in patients with schizophrenia is a complex phenomenon involving multiple factors. One of the major variables associated with noncompliance is the presence of medication-induced adverse events, such as adverse cognitive and emotional events (neuroleptic dysphoria), as well as physical ones (in particular, extrapyramidal symptoms (EPS)).

Conventional antipsychotics (CA) often cause unpleasant adverse events, including anticholinergic events, sexual dysfunction, and EPS. Furthermore, DA can deteriorate patients' quality of life since these drugs, in addition to physical adverse events, often produce cognitive, affective, and affective impairments. Patients' inability to maintain clear thinking while being on these medications may in...
tends to their daily functioning in the community life as well as their adequate occupational and psychosocial rehabilitation.

Moreover, a high percentage of patients with schizophrenia present an insufficient response to treatment when using these CA medications. When selecting an antipsychotic drug for patients hospitalized due to an acute episode of schizophrenia, a prescriber should consider a definitive treatment that will be well tolerated and accepted, while maintaining or even improving the treatment response among patients with prominent positive and agitation symptoms. Olanzapine is an atypical antipsychotic drug that has shown in clinical trials conducted among acutely exacerbated patients with schizophrenia to have superior efficacy compared to placebo. It is also compatible with haloperidol in improving positive symptoms of schizophrenia, and better than placebo and haloperidol in improving negative symp-
toms. Moreover, olanzapine appears to have a lower risk of producing EPS11 and cognitive and psychomotor impairments than CA. Since the experimental conditions of clinical trials are rarely accepted, the information obtained from these studies about the effectiveness of the new (atypical) antipsychotics under normal (real-life) treat-
ment conditions is very limited12,17. Therefore, as long as their inherent limitations are accepted, naturalistic studies allow to determine, in routine clinical conditions, the real benefits provided by new treatments such as olanzapine for patients with schi-
izophrenia.

Here we present the results from a large observational study that investigated the safety, effectiveness, and patterns of use of olanzapine in the daily clinical treat-
ment of inpatients with acutely exacerbat-
ed schizophrenia when compared with CA in order to identify a set of possible confusing factors inherent to naturalistic studies, a multivariate approach was employed.

Patients and method

Patients

This prospective, comparative, nonrandomized, open-labeled, observational study was conducted in 63 patient units, located at General Hospitals or Psy-
chiatric Units, in Spain (Hospital General Universitario de Ciudad Real; Hospital General Universitario de Alicante; Hospital Universitario de Almería; Hospital Universitario de Navarra; Hospital Universitario de Alcalá de Henares; Hospital Universitario de Salamanca; Hospital Universitario de Córdoba, among others). Patients were hospitalized because of an acute psychiatric episode who could enter this study when an antipsychotic treatment either with olanzapine or at least a CA was started following admission. Those patients to whom treatment with antipsychotic drugs was contraindicated, who were already participating in a clinical trial or undergoing treatment with atypical antipsychotics other than olanzapine were excluded.

Investigators were instructed to use their clinical judgment in choosing nonrandomized treatment and no limitation was established on clinical manage-
ment to avoid the previously mentioned restrictions. Related to clinical trials, Investigators were asked to include all eligible patients until completing a block of 6 patients in each medication group with the pur-
pose of limiting selection bias. The first oral antipsycho-
tic drug prescribed at admission determined the treatment group to which the patient was allocated. Those patients to whom treatment with an atypical antipsychotic drug was planned after admission because of lack of information regarding some of the socio-demographic or baseli-
nees was defined according to the CGI-S scale: mildly

Objective (O) response was 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 4 on the CGI-S scale.

Results

Demographic and clinical characteristics

A total of 848 inpatients treated with olanzapine (n = 463) or CA (n = 385) made up the sample of the present study. To avoid confusion in the effects of antipsychotic treatment, 57 patients from the original sample were excluded because of a change of treatment group. Among those patients, 20 were initially treated with olanzapine. These 20 patients were switched to CA because of lack of efficacy (n = 8), adverse events (n = 1), no data were available for the other 4 patients. 36 patients were initially treated with CA and were switched to olanzapine because of lack of efficacy (n = 4), insufficient efficacy (n = 8), or adverse events (n = 12); for the other 12 patients no information was avail-
able. Finally, one patient was excluded because of lack of information regarding the first antipsychotic treatment. Statisti-
cally significant differences between the OG and CA were found with regard to some of the socio-demographic or baseli-
names were carried out using a modified χ2-test to test the hypothesis of independence between the different treatment strategies. A χ2-test was used to carry out a univariate analysis to test the effect of possible confusing variables when analysing the factors that may influence the safety and ef-
fectiveness of olanzapine compared with CA. Predic-
tors of treatment response and predictors of treatment-emergent EPS were identified with logis-
tic regression models. The stratified analyses of vari-
ables were carried out with the Cochran-Mantel-Ha-
enzel test. When necessary for the description of the patterns of use of the study medications, a corre-
spondence analysis was performed.

The data were simultaneously keyed into 2 databases by different individuals and later contrasted to elimi-
nate errors. SAS versions 8.2, 10.1 and Winbugs 1.4 were used to perform the statistical analysis. A step-down linear model (Proc GLM) and a Cochran-Mantel-Ha-
enzel test were used for the verification, validation, and analysis of the data.

Classification of Diseases, 10

In this line with the protocol, neither the appro-

ality errors. SAS (SAS Institute Inc.; Cary, NC, USA; Copyright 1997; 2002) was used to analyse the clinical data-
}
the results of the multivariate analyses. It could explain the emergence of new 
monetary strategy was the only variable that 
treated with olanzapine plus CA (n = 28; 
21.19 days (range: 1-113) in the CG, and 
22.6%); the highest percentage of pa-
tients treated with olanzapine in mono-
therapy. Haloperidol was the most frequently 
treated with CA had twice the risk of EPS 
with olanzapine + CA, whereas patients 
presented a half of the risk for developing 
treated with olanzapine in monotherapy 
(risk ratio: 0.46; [95% confidence inter-
derate or severe EPS during the study 
comparable with those treated with olanzapine + CA, whereas patients 
treated with CA had twice the risk of EPS 
compared with patients treated with the 
combination.

Effectiveness
As already mentioned, treatment effecti-
veness was operationally defined as a 
combination of a decrease of at least 
40% from baseline in BPRS total score 
plus an endpoint BPRS score lower than 
18 or less than 4 on the CGI-S. Logistic 
regression analysis was performed using 
sex, age, schizophrenia subtype, number of 
previous hospitalizations, presence of posi-
tive, negative, and agitation symptoms, 
previous need for parenteral medication, and 
treatment strategy. Olanzapine, olanzapine + 
high- or low-potency CA, or CA). Treatment 
strategy was the only variable that 
could explain the emergence of new mo-
derate or severe EPS during the study 
(risk ratio: 0.46; [95% confidence inter-
val, 0.37-0.58; p < .001). Thus, patients 
treated with olanzapine in monotherapy 
presented a half of the risk for developing 
EPS as compared with patients treated 
with olanzapine + CA, whereas patients 
treated with CA had twice the risk of EPS 
compared with patients treated with the 
combination.

Additional analyses showed that the 
exception of positive symptoms) proved 
relevant to treatment response. 
The response rate in the different treat-
ment subgroups is shown in table 2. Pa-
tients treated with olanzapine in monoth-
ery achieved a significantly higher 
treatment response rate compared with 
CA monotherapy (p = 0.007), and they did 
not differ significantly from patients of the 
combined treatment subgroups (olanzap-
ine + CA, either low or high potency).

Responsiveness of psychotic symptoms was not 
homegeneous among treatment subgroups, 
the treatment response rates among pa-
tients with prominent positive symptoms in 
four treatment subgroups were analyzed 
(Table 3). Among more severe pa-
tients, results were comparable with 
those of the study group as a whole.

Patterns of use of olanzapine
With the purpose of describing the pat-
tern of use of olanzapine, a correspon-
dence as predictors of treatment 
response. None of these variables (with 
the exception of positive symptoms) pro-
ved to be relevant to treatment response.

In the OG, 124 patients (26.8%) were 
treated with a concomitant high-potency 
(n = 57; 12.3%) or low-potency (n = 67; 
14.5%) CA throughout the study, where-
as the remaining 339 patients (73.2%) 
treated with olanzapine in monother-
apy. Haloperidol was the most frequently 
treated with a concomitant high-potency 
(n = 57; 12.3%) or low-potency (n = 67;
14.5%) CA throughout the study, where-
as the remaining 339 patients (73.2%)

TABLE 1
Baseline sociodemographic and clinical characteristics of study population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OG (n = 408)</th>
<th>CG (n = 397)</th>
<th>OGm (n = 339)</th>
<th>OG vs. CG</th>
<th>OGm vs. CG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male, n (%)</td>
<td>258 (63.6)</td>
<td>226 (57.4)</td>
<td>226 (66.7)</td>
<td>0.037</td>
<td>0.009*</td>
</tr>
<tr>
<td>Age (years), mean (SD)</td>
<td>37 (11.2)</td>
<td>37 (11.3)</td>
<td>37 (11.2)</td>
<td>0.940</td>
<td>0.940</td>
</tr>
<tr>
<td>Duration of illness (years), mean (SD)</td>
<td>10.5 (9.2)</td>
<td>13.3 (9.7)</td>
<td>10.0 (9.1)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Duration of illness (months), mean (SD)</td>
<td>10.5 (9.2)</td>
<td>13.3 (9.7)</td>
<td>10.0 (9.1)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Schizophrenia subtype, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paranoid</td>
<td>90 (21.9)</td>
<td>87 (21.9)</td>
<td>85 (25.1)</td>
<td>0.710</td>
<td>0.054</td>
</tr>
<tr>
<td>Undifferentiated</td>
<td>63 (15.4)</td>
<td>61 (15.5)</td>
<td>57 (16.8)</td>
<td>0.902</td>
<td>0.902</td>
</tr>
<tr>
<td></td>
<td>135 (33.3)</td>
<td>128 (32.4)</td>
<td>131 (38.8)</td>
<td>0.679</td>
<td>0.679</td>
</tr>
<tr>
<td>Number of previous hospitalizations, mean (SD)</td>
<td>3.9 (3.6)</td>
<td>4.3 (3.9)</td>
<td>4.1 (3.8)</td>
<td>0.469</td>
<td>0.469</td>
</tr>
<tr>
<td>% treated with a concomitant medication</td>
<td>105 (26.0)</td>
<td>106 (26.7)</td>
<td>102 (30.0)</td>
<td>0.389</td>
<td>0.389</td>
</tr>
<tr>
<td>Baseline CGI-S score, mean (SD)</td>
<td>5.0 (0.8)</td>
<td>5.2 (0.9)</td>
<td>5.0 (0.8)</td>
<td>0.002</td>
<td>0.002</td>
</tr>
<tr>
<td>Baseline BPRS total score, mean (SD)</td>
<td>45.5 (12.3)</td>
<td>45.5 (12.3)</td>
<td>45.5 (12.3)</td>
<td>0.992</td>
<td>0.992</td>
</tr>
<tr>
<td>CGI-S</td>
<td>37.5 (9.7)</td>
<td>37.8 (9.8)</td>
<td>37.7 (9.6)</td>
<td>0.951</td>
<td>0.951</td>
</tr>
<tr>
<td>CGI-S plus score, mean (SD)</td>
<td>7.4 (4.0)</td>
<td>7.0 (4.1)</td>
<td>7.0 (4.1)</td>
<td>0.696</td>
<td>0.696</td>
</tr>
<tr>
<td>CGI-S negative score, mean (SD)</td>
<td>47.5 (14.8)</td>
<td>46.5 (16.7)</td>
<td>44.7 (14.4)</td>
<td>0.005</td>
<td>0.005</td>
</tr>
<tr>
<td>Baseline NOSIE score, mean (SD)</td>
<td>139 (30.0)</td>
<td>94 (24.4)</td>
<td>101 (29.8)</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001*</td>
</tr>
<tr>
<td>Baseline presence of EPS, n (%)</td>
<td>121 (29.8)</td>
<td>106 (26.7)</td>
<td>117 (34.4)</td>
<td>0.104</td>
<td>0.104</td>
</tr>
</tbody>
</table>

TABLE 2
Response rates in the treatment subgroups

<table>
<thead>
<tr>
<th>Treatment subgroup</th>
<th>Rate of treatment response</th>
<th>RR of treatment response vs. OC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA monotherapy</td>
<td>61.2% (240/381)</td>
<td>0.86 (0.78-0.95)*</td>
</tr>
<tr>
<td>DL2 + CA (low potency)</td>
<td>60.0% (188/313)</td>
<td>0.88 (0.80-0.96)*</td>
</tr>
<tr>
<td>DL2 + CA (high potency)</td>
<td>64.6% (166/255)</td>
<td>0.97 (0.90-1.04)*</td>
</tr>
</tbody>
</table>

TABLE 3
Treatment response rates among patients with prominent positive symptoms

<table>
<thead>
<tr>
<th>Treatment subgroup</th>
<th>Rate of response in PPS(+)</th>
<th>RR of treatment response vs. OC (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CA monotherapy</td>
<td>70.7% (140/197)</td>
<td>0.87 (0.77-0.96)*</td>
</tr>
<tr>
<td>DL2 + CA (low potency)</td>
<td>67.5% (121/180)</td>
<td>0.95 (0.87-1.05)</td>
</tr>
<tr>
<td>DL2 + CA (high potency)</td>
<td>75.5% (76/101)</td>
<td>1.04 (0.98-1.10)*</td>
</tr>
</tbody>
</table>

**Note:** PPS(+) = prominent positive symptoms; OC = olanzapine; CA = conventional antipsychotic; DL2 = olanzapine plus CA; OG = olanzapine group; CG = control group; OGm = olanzapine in monotherapy; CGI-S = Clinical Global Impressions-Severity of Illness; BPRS = Brief Psychiatric Rating Scale; NOSIE = Nurses Observation Scale for In-patient Evaluation; EPS = extrapyramidal symptoms; SD = standard deviation; OGm = olanzapine in monotherapy; CA = conventional antipsychotic(s); OLZ = olanzapine. * p = 0.025.
A multivariate analysis of a large naturalistic study in the hospital setting.

CAÑAS F, ET AL. SAFETY, EFFECTIVENESS, AND PATTERNS OF USE OF OLANZAPINE OF ACUTE SCHIZOPHRENIA: A MULTIVARIATE ANALYSIS OF A LARGE NATURALISTIC STUDY IN THE HOSPITAL SETTING

A logistic regression analysis was performed to assess how the dosage of olanzapine affected treatment response. Because severity of illness and agitation determined the pattern of treatment before the initial dose was prescribed, baseline BPRS total score, presence of agitation, treatment strategy (olanzapine in monotherapy or olanzapine combined with low- or high-potency CA), and level of initial dosage were used as predictors of treatment response.

A logistic regression model detected none of the variables as a predictor of treatment response. Because severity of illness and agitation determined the pattern of treatment before the initial dose was prescribed, baseline BPRS total score, presence of agitation, treatment strategy (olanzapine in monotherapy or olanzapine combined with low- or high-potency CA), and level of initial dosage were used as predictors of treatment response. The logistic-regression model detected none of the variables as a predictor of treatment response.

A Cochran-Mantel-Haenszel test controlling for agitation did not detect differences in the treatment response with respect to the levels of mean modal doses of olanzapine (p = 0.829). No significantly different treatment response rates were found for the levels of olanzapine dosages even when taking into account whether dosages were maintained or increased throughout the study (Cochran-Mantel-Haenszel test, p = 0.286). Considering solely those patients for whom olanzapine dose was increased, a trend towards a higher treatment response rate with regard to augmentation of dosage was detected (Cochran-Mantel-Haenszel test, p = 0.066).

The more frequently prescribed initial dosage level ranged between 10 and 15 mg/day (46.66%), which was augmented up to 20 mg/day in the majority of cases (57.14%).

Extrapyramidal symptoms and treatment response

We were also interested in looking at a parameter that could combine information on treatment effectiveness and tolerability with regard to EPS (fig. 1). Thus, we searched for a point of equilibrium between treatment response and absence of EPS. The percentage of treatment-responsive patients without new treatment-emergent EPS was stratified by treatment strategy controlling for severity of illness (table 4). A statistically significant association between treatment response and the rate of treatment-emergent EPS was detected for the OGM subgroup (Cochran-Mantel-Haenszel test, p = 0.002), whereas no association could be detected in the CG (Cochran-Mantel-Haenszel test, p = 0.474) or in the subgroup treated with olanzapine plus CA (p = 0.480).

TABLE 4 Percentage of treatment-responsive patients with schizophrenia without new extrapyramidal symptoms for each subgroup of treatment

<table>
<thead>
<tr>
<th>Severity of Illness</th>
<th>CG (n = 383)</th>
<th>OLM + CA (n = 126)</th>
<th>OLM* (n = 383)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (score 1-3)</td>
<td>51.3%</td>
<td>68.9%</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>30.5%</td>
<td>67.5%</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>33.6%</td>
<td>64.0%</td>
<td></td>
</tr>
</tbody>
</table>

A Cochran-Mantel-Haenszel test controlling for severity of illness, level of positive or agitation symptoms, duration of illness, number of previous hospitalizations, or need of parenteral medication, as shown by the logistic regression analysis. The only variable significantly associated with the emergence or worsening of EPS was the treatment strategy. The effectiveness of olanzapine in acutely exacerbated inpatients with schizophrenia was confirmed independently of the illness severity and characteristics. Patients treated with olanzapine monotherapy achieved significantly higher response rates compared with CA-treated patients. Treatment response rates did not differ significantly between patients treated with OGM and those treated with olanzapine + CA. The results were similar when the analyses were repeated in the subgroup of patients with prominent positive symptoms, thus supporting the idea that this finding is not due to a lower degree of baseline severity of illness in the OGM group. This finding is consistent with previous reports on the effectiveness of olanzapine in severely psychotic patients with schizophrenia, supporting the idea that olanzapine can be used as a first-line treatment in acutely psychotic patients with schizophrenia in the hospital setting.

Once the effectiveness of olanzapine was demonstrated, we were interested in knowing the optimal dosage for obtaining optimal response.
response. In a first step, we studied the patterns of initial olanzapine prescription. The best model revealed 2 different patterns related to symptoms severity and presence of agitation at the time of hospital admission. More severely ill and agitated patients tended to be treated by their psychiatrists with olanzapine doses greater than 20 mg/day plus CA, while those patients with a lower symptom severity and lack of agitation tended to be treated with olanzapine in monotherapy with doses ranging between 10 and 15 mg/day.

No significant association between olanzapine dose and treatment response was observed in this study, even when the analyses were adjusted for symptom severity, presence of agitation, and use of concomitant CA. Thus, this study showed that olanzapine is effective in severe psychotic patients with schizophrenia regardless of the dose and use of concomitant CA.

Our final step in the analysis of the relationship between olanzapine use patterns and treatment response was the assessment of the dose modification during the hospital stay. Among those patients for whom olanzapine dose was increased, we found a trend towards a higher treatment response rate in relation to dose augmentation, which was independent of the presence of agitation. This could imply that olanzapine augmentation may be a good therapeutic strategy for patients with schizophrenia admitted to the hospital. Unfortunately, the design of the study did not allow to adequately establish a temporal relationship between the dosage of olanzapine and its effectiveness.

The final objective of this study was to combine information on safety, with regard to EPS, and effectiveness, to establish the best global treatment strategy. We found, controlling for the illness severity, that olanzapine in monotherapy represented the best choice (DGm subgroup) at lower doses (around 5 mg/day) and a low rate of EPS (11.2%). Treatment with CA in monotherapy led to a decrease in the response rate, and, at the same time, an increase in the rate of presence of new EPS or of worsening of existing EPS. On the other hand, the use of olanzapine with concomitant CA did not significantly affect the treatment response rate, increasing the rate of EPS.

Relapse in schizophrenia has been strongly associated with noncompliance, mostly due, in the majority of cases, to the presence of EPS. Thus, the prescription during the hospital stay of an effective and well-tolerated antipsychotic may prevent relapse and subsequently ensure the continuity of an adequate psychosocial rehabilitation. In this study, olanzapine, especially when used in monotherapy, induced a low rate of clinically relevant EPS. Furthermore, the search for the point of equilibrium between effectiveness and absence of EPS pointed out that even severely ill patients in the DGm subgroup achieved the highest rate of response without generating new EPS.

A naturalistic study design allows us to discover treatment patterns used by a wide spectrum of psychiatrists working in acute inpatient units. It is worthy of note that in the current study, the choice of a treatment strategy based on combinations of drugs was done at the beginning of treatment and was, therefore, based more on a priori assumptions than on controlled data. When the study was performed in 1999, olanzapine was a relatively new antipsychotic drug in Spain, and little additional information (other than that provided by clinical trials) about the real benefits of its use was available. Thus, it is very likely that some investigators preferred to use well-known drugs, especially in more severely ill patients. Results presented here may help prescribers reconsider their choice of treatment strategy.

Several limitations are inherent to any observational study, such as selection bias due to lack of randomization, difficulties in establishing unambiguous causal relationships, and probable underreporting of adverse events compared with clinical trials. However, despite these limitations, naturalistic studies allow us to study what is really happening in the clinical setting without the constraints of experimental designs. Moreover, in the present study, a multivariate statistical approach was used to minimize the effect of possible confounding variables, thus allowing more robust conclusions.

In summary, after accepting the limitations of a naturalistic study and taking the results of the present study into account, we consider that olanzapine by itself constitutes a greater risk of developing EPS. The results of this study allow to adequately establish a temporal relationship between the dosage of olanzapine and treatment response. This could imply that olanzapine augmentation may be a good therapeutic strategy for patients with schizophrenia, especially when depression is present or the presence of agitation. This could indicate that olanzapine by itself constitutes a greater risk of developing EPS. The results of this study allow to adequately establish a temporal relationship between the dosage of olanzapine and treatment response. This could imply that olanzapine augmentation may be a good therapeutic strategy for patients with schizophrenia, especially when depression is present or the presence of agitation. This could imply that olanzapine augmentation may be a good therapeutic strategy for patients with schizophrenia, especially when depression is present or the presence of agitation. This could imply that olanzapine augmentation may be a good therapeutic strategy for patients with schizophrenia, especially when depression is present or the presence of agitation.

Acknowledgments
This work was sponsored by Lilly Research Laboratories, Alcobendas, Spain.

Psychiatrists participating in the study
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REFERENCES