The European schizophrenia outpatient health outcomes (SOHO) study: baseline findings of the Spanish sample

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Estudio observacional paneuropeo de la efectividad de la olanzapina frente a otros antipsicóticos (SOHO): resultados basales de la muestra española

Summary

Introduction. *To describe the baseline findings and study population of the Spanish sample of the Schizophrenia Outpatient Health Outcomes (SOHO) Study.*

Method. *The SOHO study is an ongoing, large, prospective, long-term observational study of schizophrenia treatment in 10 European countries. The study population consists of outpatients who initiate therapy or change to a new antipsychotic.*

Results. *A total of 86 investigators enrolled 2,020 in Spain (10,972 patients in Europe). 64 % of patients were men and the mean age was 38.7 years. The Spanish SOHO study sample had considerable functional impairment at baseline. The main reason for change of therapy was lack of effectiveness followed by intolerability. Patients included in the study and those receiving their first antipsychotic for schizophrenia are most likely to receive an atypical agent.*

Conclusion. *The Spanish SOHO study population appears to represent the Spanish outpatients with schizophrenia in whom a treatment decision is required. Baseline findings reflect Spanish clinical practice with respect to patients treated with individual antipsychotics.*

Key words: *Observational. Antipsychotic agents. Schizophrenia. Outpatients. Utilization patterns.*

Resumen

Introducción. *El objetivo principal del estudio SOHO es evaluar la efectividad y seguridad de olanzapina frente a otros antipsicóticos en el tratamiento de pacientes esquizofrénicos ambulatorios en la práctica clínica habitual. Se presentan los datos demográficos y las características clínicas y de tratamiento basales de la muestra española incluida en el estudio.*

Método. *El SOHO es un estudio observacional, prospectivo, longitudinal (de 3 años de seguimiento), no intervencionista y abierto que se lleva a cabo actualmente en 10 países europeos. El diseño de este estudio permite evaluar el impacto en la efectividad y seguridad asociada al tratamiento de pacientes esquizofrénicos. La población examinada está compuesta por pacientes ambulatorios que inician el tratamiento con un antipsicótico o lo cambian por otro diferente.*

Resultados. *En total, 86 investigadores españoles reclutaron a 2.020 pacientes (en toda Europa se reclutó a 10.972). El 64 % pertenecía al sexo masculino y el promedio de edad era de 38,7 años. La muestra española del estudio SOHO presentaba una alteración funcional considerable en condiciones basales. El motivo principal del cambio de tratamiento fue la falta de eficacia, seguido de problemas de tolerabilidad. Los pacientes incluidos en el estudio y los que recibieron por primera vez un antipsicótico para tratar la esquizofrenia tienen más probabilidad de ser tratados con un antipsicótico atípico.*

Conclusión. *Los 2.020 pacientes incluidos en España suponen una muestra representativa que permitirá realizar análisis de efectividad, seguridad y patrones de utilización de la olanzapina y otros antipsicóticos en el contexto español.*

Palabras clave: *Observacional. Antipsicóticos. Esquizofrenia. Atención ambulatoria. Patrones de utilización.*

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INTRODUCTION

The introduction of anti-psychotic drugs during the 1950's represented a great step forward in the treatment of schizophrenia and other psychoses. The limi-

tations of these drugs, both in terms of effectiveness and their safety profile have, however, become evident over time. A high percentage of schizophrenic patients present an insufficient response to treatment with this conventional anti-psychotic medication[1] and up to 60% relapse one year after therapy[2]. Moreover, the high incidence of side effects associated with conventional anti-psychotic drugs, particularly the extra-pyramidal symptoms (EPS), has greatly contributed to poor compliance among patients and therefore high relapse rates[3]. All of these factors contribute to repeated hospital admissions and to progressive social and occupational dysfunction. These therapeutic limitations have made essential the availability of more effective and better-tolerated drugs.

Atypical antipsychotic drugs have been available for the treatment of schizophrenia for over a decade. Evidence from randomized controlled trials (RCTs) appears to indicate that compared with typical antipsychotic agents, atypical antipsychotics provide similar or improved efficacy in terms of positive symptoms while exhibiting a more favorable EPS profile. Atypical agents also provide increased efficacy against negative and cognitive symptoms and reduce the risk of tardive dyskinesia[4-10].

Randomized clinical trials (RCTs) are regarded as the gold standard for comparing efficacy and safety of different therapeutic options. However, RCTs may not always answer the questions asked by clinicians in actual practice[11,12]. RCTs are carried out in accordance with very strict criteria regarding the selection of patients and researchers, thus limiting the generalization of their conclusions[13]. Additionally, the design of some RCTs may not always be adequate. A recent review evaluated the quality of the 2,000 controlled trials carried out in the area of schizophrenia over the past 50 years[14]. The conclusions are disappointing: studies were of short duration (only 19% had a 6 month follow-up, and in 54% this was less than 6 weeks), with a small number of patients (65 on average), and rarely community based (14%). Reports of only 20 trials (1%) raised the issue of the statistical power of the study, which addresses the adequacy of the sample size. Moreover, the clinical studies often have important differences in design (different dose ranges, duration, measures of efficacy and safety, etc.) that greatly complicate the direct comparison between different antipsychotic drugs[15]. RCT dosing protocols are usually predetermined, so the researcher ability to vary doses is often limited. Moreover, most clinical trials with antipsychotics have excluded patients with concomitant organic or psychiatric diseases, especially substance abuse or dependency disorders which have a high prevalence among the schizophrenic population[16]. In the same way, greater therapeutic compliance and restrictions on the concomitant use of other antipsychotics in RCTs may contribute to differences between recommended doses and doses used in actual clinical practice.

Such issues reinforce the need to carry out observational studies to answer unresolved questions and to compliment information from RCTs. Pharmacoepidemiological studies can be very useful for improving knowledge of the actual use of drugs after their commercialization[17]. Among other advantages, naturalistic studies can help to determine whether the clinicians' actual use patterns match with manufacturers' recommendations, which are based on information obtained from RCTs. Moreover, naturalistic studies may provide insight to the reasons for discrepancies when they exist. Thus, there is clearly a need for large, prospective, long-term, observational studies of schizophrenia treatment.

The Schizophrenia Outpatient Health Outcomes (SOHO) Study has been initiated to address this need by providing crucial information on how treatment impacts outcome. SOHO, a prospective, observational study, lasting for 3 years, covering 10 european countries, is the largest study in schizophrenia conducted in Europe, collecting data on the impact by the therapies on the patients' functionality and quality of life in addition to clinical and pharmacological information[18]. This paper describes the baseline characteristics and comparability of patients recruited in Spain (n = 2,020).

METHOD

Study design

The SOHO study is an ongoing, 3-year, prospective, observational study of the treatment of schizophrenia in Europe. The study is being conducted currently in 10 European countries (Denmark, France, Germany, Greece, Ireland, Italy, the Netherlands, Portugal, Spain and the UK). The recruitment period extended from 1 September 2000-31 December 2001. More than 1000 psychiatrists are participating in the study (86 in Spain). The SOHO study design is outlined briefly below.

Participating psychiatrists offered enrolment at their discretion to patients who met the following entry criteria:

- Initiating or changing antipsychotic medication for the treatment of schizophrenia.
- Presenting within the normal course of care in the out-patient setting or in the hospital when admission was planned for the initiation or change of antipsychotic medication, with discharge planned within 2 weeks.
- At least 18 years of age.
- Not participating in an interventional study.

Patients

Patients were included regardless of whether the new antipsychotic drug substituted a previous medication or was an addition to existing treatment, and regardless of the reason for the treatment change. Investigators were instructed to make treatment decisions independent of the study and then to evaluate whether patients were eligible for inclusion based on the entry criteria.

Oral patient consent was required, with written consent as required by local regulations.

The SOHO study was designed to provide two patient cohorts of approximately equal size:

— Patients who initiated therapy with or changed to olanzapine.
— Patients who initiated therapy with or changed to a non-olanzapine antipsychotic.

Schedule of assessments

Efficacy and safety information are planned to be captured along the 3 years of the study with the following visits schedule: baseline, 3 months, 6 months, and all further visits up to 36 months each 6 months apart.

Objectives

The primary objective of the study is to assess the costs and outcomes of schizophrenia treatment using antipsychotics with a specific focus on the atypical antipsychotic olanzapine. Secondary objectives are to understand the pharmacological treatment patterns for schizophrenia, to assess how these patterns are associated to olanzapine versus other antipsychotics, and to evaluate how these patterns are associated with outcomes.

The data collected were similar to those usually collected in routine clinical practice, including patient demographics, medical resource use, functional status, clinical status, medication use, tolerability, patient and physician-reported compliance, sexual function, alcohol and substance abuse and quality of life

Measurements

Baseline characteristics evaluated included demographics, clinical status, quality of life, global activity and social functioning, tolerability, antipsychotic and other medication, compliance or adherence to prescribed therapy, work, social and living conditions, criminality, violence and victimization, medical resource use, costs and suicide attempts.

Clinical severity was assessed using a scale based on the clinical global impression (CGI) (Guy, 1976) that evaluated positive, negative, cognitive, depressive and overall symptoms on the day of assessment. This was subsequently expanded and validated as the CGI-SCH[19], a scale that evaluates symptom severity during the week preceding the day of assessment and symptom change since the previous evaluation. While the CGI-severity score scale rates overall severity, the CGI-SCH scale is a 4-item scale that assesses positive, negative, cognitive and depressive symptoms. Both are physician-rated scales with values ranging from 0 (not ill) to 6 (among the most severely ill patients). The scale aims to translate clinical judgment into ratings that reflect the diversity of symptoms present in schizophrenia. As the ratings are based on clinical judgment and the assessment is not time consuming to administer, the scale is appropriate for use in observational studies and in routine clinical practice.

Quality of life was assessed by means of the Spanish version of the EuroQol (EQ-5D)[20]. It is a self-administered instrument, applicable in a wide variety of states of health and treatments, and validated worldwide. EuroQol was chosen on the basis of its generic character, brevity, and proven validity for detecting health-related quality of life differences between patients with different degrees of severity of schizophrenia[22]. The first part (EuroQoL-1) describes the health status itself in terms of five dimensions (mobility, personal care, daily activities, pain/discomfort, and anxiety/depression) each of which includes three degrees of severity (1: no problem; 2: some/moderate problems; 3: many problems). The second part is the Visual Analog Scale (VAS), consisting of a 20 cm. long, vertical graph, in the shape of a thermometer, the ends of which are labeled, «worst state of health possible» and «best state of health possible», and with scores of 0 to 100, respectively. Subjects make a mark indicating their state of health.

For assessing global activity the GAF scale was used[22].

Social functioning was assessed using the last version of the social functioning scale designed by Birchwood et al. as a measurement to evaluate the crucial areas directly related with the outpatient status of those schizophrenic patients[23]. These areas include: *a)* isolation (time isolately, conversation beginning, social avoiding); *b)* interpersonal conduct (number of friends, heterosexual contacts, communication quality); *c)* prosocial activities (sports, etc.); *d)* free time (hobbies, interests); *e)* independence, and competence (independent performance); *f)* independent execution (Independent life); *g)* employment and occupation (daily compromise for a productive work within a structured program). This scale was used just in the Spanish population of the study.

Sample Size

The sample size calculation was based on the minimum number of patients to show statistical significance at the 13% level of difference in mean cost for the pan-European analysis, requiring a total of 10,800 patients (5,400 per arm).

Statistical analysis

Categorical parameters have been summarized with both absolute and relative frequencies. Characteristics based on a numerical scale have been summarized with number of observations, mean value, standard deviation, standard error, median and interquartilic range.

For testing the homogeneity between treatment groups (olanzapine versus others) these parameters have been compared with the Student's *t*-test (quantitative) or the Mantel-Haenszel χ^2 test (categorical) with a 2-sided alpha error < 0.05.

No imputation methods were applied and all descriptions were obtained from the Intention to Treat population.

The statistical analysis has been performed with the SAS System version 8[24].

RESULTS

A total of 10,972 patients were enrolled into the paneuropean study, with a total of 2,020 patients (19.8 %) recruited in Spain by 86 psychiatrists Investigators (table 1), from February to December 2001. Of these 2,020 patients recruited in Spain, 27 (1.3 %) were excluded from this and future analyses due to failure to meet entry criteria or failure of treatment cohort allocation. The results presented here are related to the remaining 1,993 patients.

In accordance with the study design, approximately 50 % of patients received olanzapine at baseline (54 %). Of those 901 patients within the Control Group, 52 % were using risperidone, 20 % quetiapine, 11 % depot typical, and 10 % PO typical (table 2).

The mean age of the Spanish patients was 38.7 years (standard deviation: 12.9), with 36 % women. Baseline comparisons between olanzapine group and control group showed no statistical heterogeneity for most of the measurements; however, a statistically significant difference was observed for BMI and percentage of first episodes. A slightly lower mean BMI and a higher percentage of first episodes in the olanzapine group were observed (table 3).

Upon presentation 76.7 % of patients were taking antipsychotic medication at baseline, 54.6 % of them were taking only typicals , the oral route was used in 67 %, and the depot route in 20 %. (the most frequent was haloperidol 49.9 %) and the other 34 % only atypicals (the most frequent was risperidone: 64.3 %) a 9,3 % of patients were taking both typical and atypicals. 23,3 % of patients enrolled were not taking antipsychotic treatment at baseline (8.5 % were first episode).

TABLE 1. Characteristic of the Spanish psychiatrists participating in the SOHO study

Characteristic	*Value*
Investigators	86
Mean age (SD)	41.9 (6.53)
Gender (% women)	27.9
Practice type (%)	
Public	63.5
Private	4.7
Combined (public and private)	31.8
Practice location (%)	
Urban	75.3
Non-urban	24.7
Years as psychiatrist (median)	12.0
Number of patients enrolled by investigators (%)	
1 to 5	21.2
6 to 10	45.3
11 to 15	10.0
16 or more	23.5

TABLE 2. Medication initiated at baseline in the Spanish sample of the SOHO study

	N (%)
Olanzapine group	1,092 (54.1)
Control group	901 (45.9)
Risperidone	467 (51.8)
Quetiapine	183 (20.3)
Depot typical	98 (10.9)
PO typical	94 (10.4)
Clozapine	34 (3.8)
Two or more typical	22 (2.5)
Other atypical	3 (0.3)

In accordance with the study design, approximately 50 % of the patients received olanzapine at baseline (54 %). The atypical antipsychotics, risperidone and quetiapine, were the most frequently prescribed antipsychotics in the control group (51.8 % and 20.3 % respectively). 10.9 % of the patients were treated with depot typicals and 10.4 % with oral typicals. 3.8 % received clozapine and 2.5 % two or more antipsychotics.

A higher proportion of patients treated with olanzapine or risperidone were classified as experiencing their first episode of schizophrenia compared with patients treated with other antipsychotics.

The median olanzapine, risperidone, quetiapine and haloperidol doses upon presentation were 10, 6, 300 and 10 mg respectively, with 34 % of those patients with olanzapine with a dose equal or greater than 20 mg. These patients with high dose of olanzapine presented significantly higher scores (Mantel-Haenszel; $p < 0{,}001$) on the clinical severity symptoms at baseline, both specific and overall. Of those patients receiving typical antipsychotics, 61 % were treated with haloperidol.

Around 75 % of the patients were enrolled into the study just after an antipsychotic change mainly due to lack of effectiveness (around 60 %) and intolerability (over 30 %) (fig. 1).

The main reason for change of therapy was lack of effectiveness (35 % olanzapine, 39 % risperidone, 43 % haloperidol, 64 % quetiapine, 47 % clozapine), followed by intolerability and patient's request (fig. 1).

No differences were detected by treatment group upon presentation in the clinical status (fig. 2) (CGI-SCH overall and other CGI-SCH subscales; Mantel-Haenszel test; $p = 0.542$), but for the depressive subscale with lower values in control group versus olanzapine group. Almost 30% of the patients attempted to suicide ever, with a mean of 2.3 attempts (SD: 3.3), and this figure goes to 6 % if only the last 6 months are considered.

TABLA 3. Baseline characteristics of the Spanish patients participating in the SOHO study

Characteristic[a]	*Olanzapine group (n = 1.092)*	*Control group (n = 901)*	*Risperidone (n = 467)*	*Quetiapine (n = 183)*	*Typical (n = 192)*	*Homogeneity p-value*[b]
Gender (% males)	712 (65.3%)	558 (52.0%)	300 (64.4%)	111 (60.7%)	112 (58.3%)	0.098[c]
Age (years: mean [SD])	38.6 (13.4)	38.8 (12.3)	39.1 (12.6)	39 (11.7)	39.6 (12.7)	0.805[d]
Body mass index (mean [SD])	25.9 (4.3)	26.8 (5.0)	26.7 (5.1)	27.7 (4.9)	26.7 (4.9)	< 0.001[d]
Time from first diagnostic (years: mean [SD])	11.0 (11.6)	11.2 (11.3)	11.5 (11.9)	11.4 (11.4)	11.3 (10.6)	0.596[d]
First episode (%)	120 (11.0%)	51 (5.7%)	38 (8.2%)	5 (2.7%)	6 (3.1%)	< 0.001[c]
CGI-SCH overall (1 to 7) (mean [SD])	3.5 (0.9)	3.5 (1.0)	3.5 (0.9)	3.5 (1.1)	3.5 (1.0)	0.501[d]
EQ-5D (0 to 2) (mean [SD])	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.6 (0.3)	0.126[d]
VAS (0 to 100) (mean [SD])	49.4 (18.5)	50.1 (19.7)	49.6 (19.6)	50 (20.4)	52.5 (19.4)	0.460[d]
GAF (0 to 100) (mean [SD])	48.5 (14.0)	47.7 (14.1)	47.9 (14.0)	49.5 (14.9)	47.3 (13.9)	0.222[d]

[a] Only the main treatment groups have been considered within this summary table. [b] Between olanzapine group and control group. [c] χ^2 test. [d] t test.

Regarding quality of life assessed by means of EURO-QoL patients presented no differences between groups related to the Health Status with a mean VAS around 50 (fig. 3).

Similarly between treatment groups the dependency/abuse of both alcohol or other substances affected in the past to 16% of the patients, and currently to 4%, with hostility in the past in 36% of the patients, 8% arrests, and 3% victim of violent crime.

The work and social functioning scale evaluates current problems related to the last 4 weeks. Almost 25% of patients present current problems in the relationship with spouse/partner, and 42% of patients presented independent living problems during past 4 weeks. Up to 32% of the patients presented no engagement in social activities during past 4 weeks, while no more than 16% of the patients presented problems related to paid employment during past 4 weeks. In addition, sexual problems during past 4 weeks were assessed in 32% of the patients.

Regarding the use of resources in the last 6 months, 34% of patients registered inpatient admissions, 23% day-hospital visits, and 96% outpatient visits.

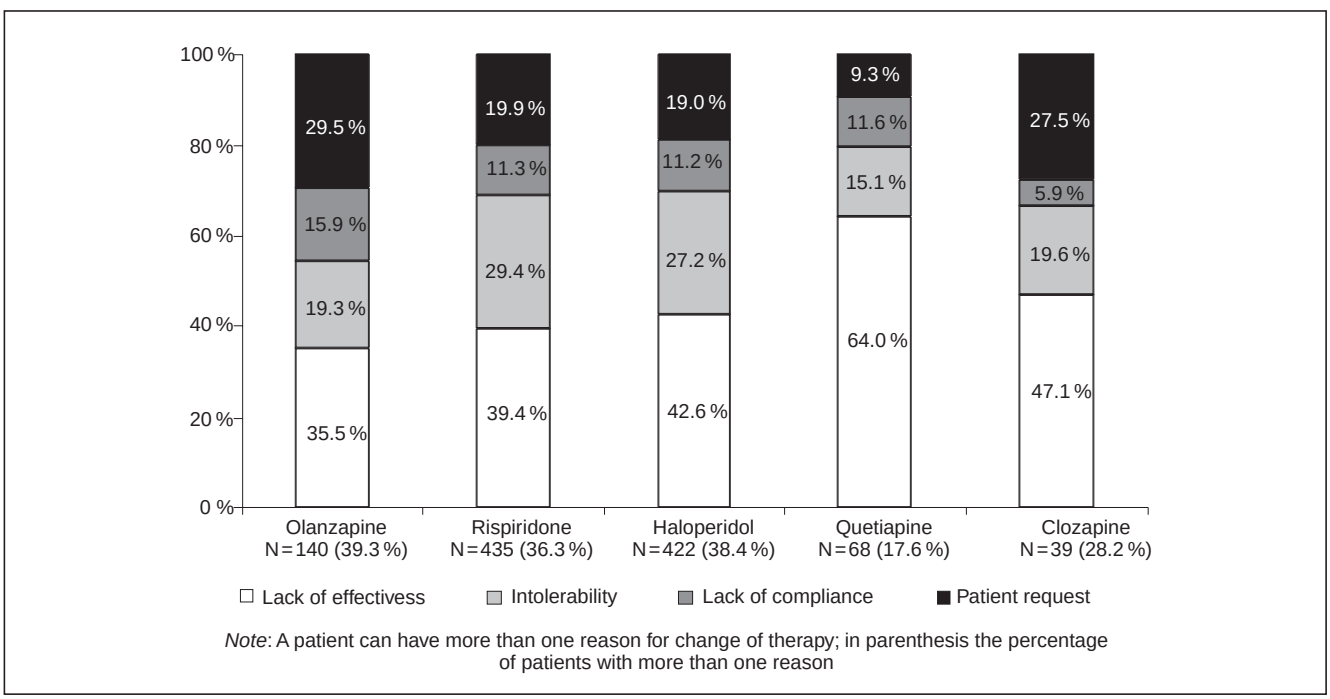

Figure 1. Reason for change of therapy of the Spanish sample.

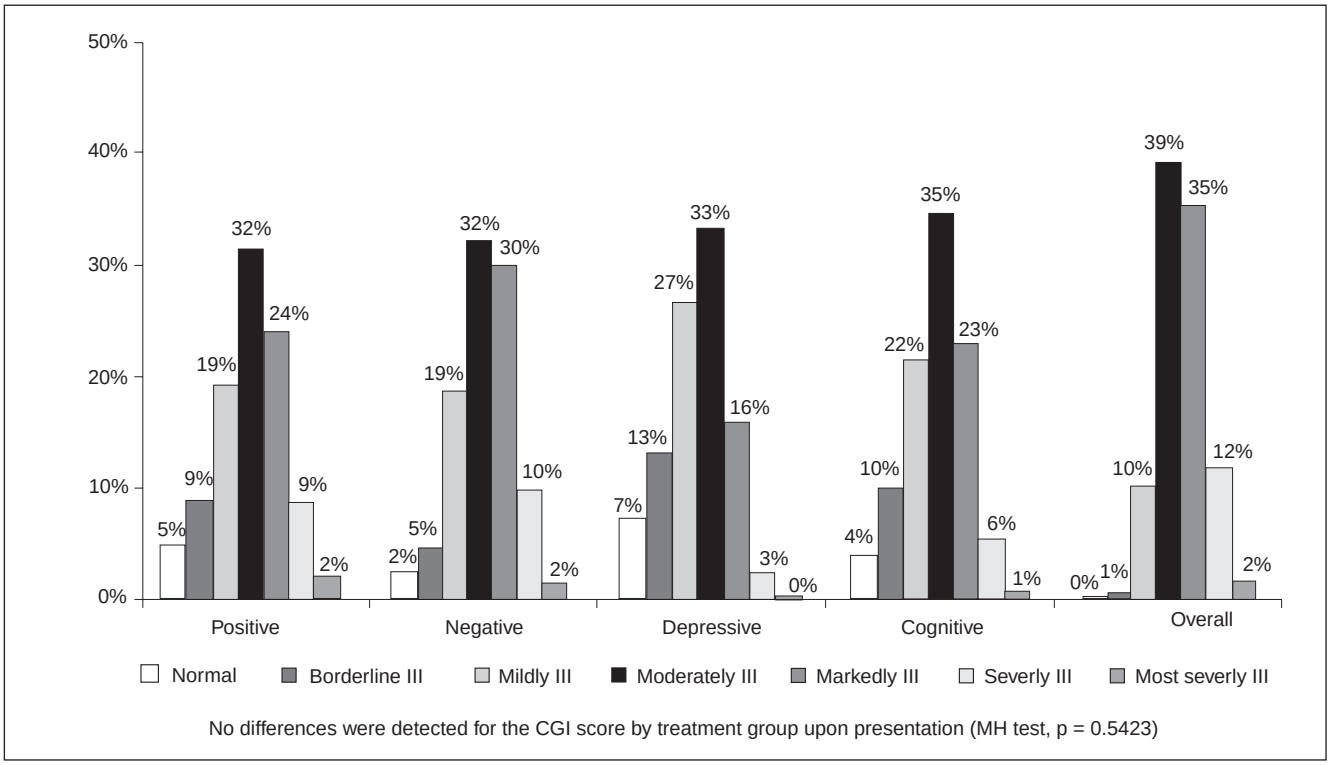

Figure 2. Clinical severity: CGI-SCH overall scale and subscale.

Among the concomitant medications (65 % before being included in the study, and 59% after inclusion), anxiolytics/hypnotics were the most frequently used (43 %), followed by anticholinergics (31 %), antidepresants (16%) and mood stabilizers (6%). The only significant change after inclusion was related to the anticholinergic treatments which changes from 31 % of the patients to 19% ($p < 0.001$).

The compliance assessment of past 4 weeks detected that, from the investigators point of view 75% of the patients almost always took the medication. Following the investigators assessment, this figure increases to 81 %.

DISCUSSION

The SOHO study is a prospective observational study of antipsychotic treatment for schizophrenia. A total of 10,972 patients were enrolled from ten European countries, of which 2,020 were included in Spain.

The enrolling Spanish psychiatrists differed in terms of their practice location and setting; most psychiatrists practiced in the public sector, which is consistent with mental health service availability in Spain[25].

The proportion of women and the mean age of patients enrolled in the study were consistent with prevalence-based samples of individuals with schizophrenia treated in the outpatient sector in Spain[26] which contributed to the comparability of the results with those from previous studies.

Additionally, the baseline homogeneity of the patients treated with antipsychotics other than olanzapine made it possible to consider them as a singre control group for comparison purposes versus the olanzapine group.

On enrolment into the SOHO study, treatment for most patients was initiated with an atypical antipsychotic. This was only partly due to the study design (approximately 50 % of the patients started therapy with olanzapine); even in the control group, treatment for most patients was initiated with an atypical antipsychotic. Furthermore, most patients in the control group who received an antipsychotic for the first time for schizophrenia on entry into the SOHO study also received an atypical antipsychotic. Given that atypical antipsychotics are used more often than typicals in the treatment of schizophrenia in Spain, these findings might be considered as not surprising. Another factor that may contribute to this prescribing pattern is that most patients in the SOHO study population were receiving a typical antipsychotic in the 6 months before enrolment, and a change in antipsychotic was required on enrolment. Recent schizophrenia treatment guidelines recommend the use of atypical antipsychotics both for first-line treatment and in patients in whom treatment with a typical antipsychotic has failed[27,28]. The Spanish sample of SOHO study baseline treatment patterns reflects these treatment recommendations.

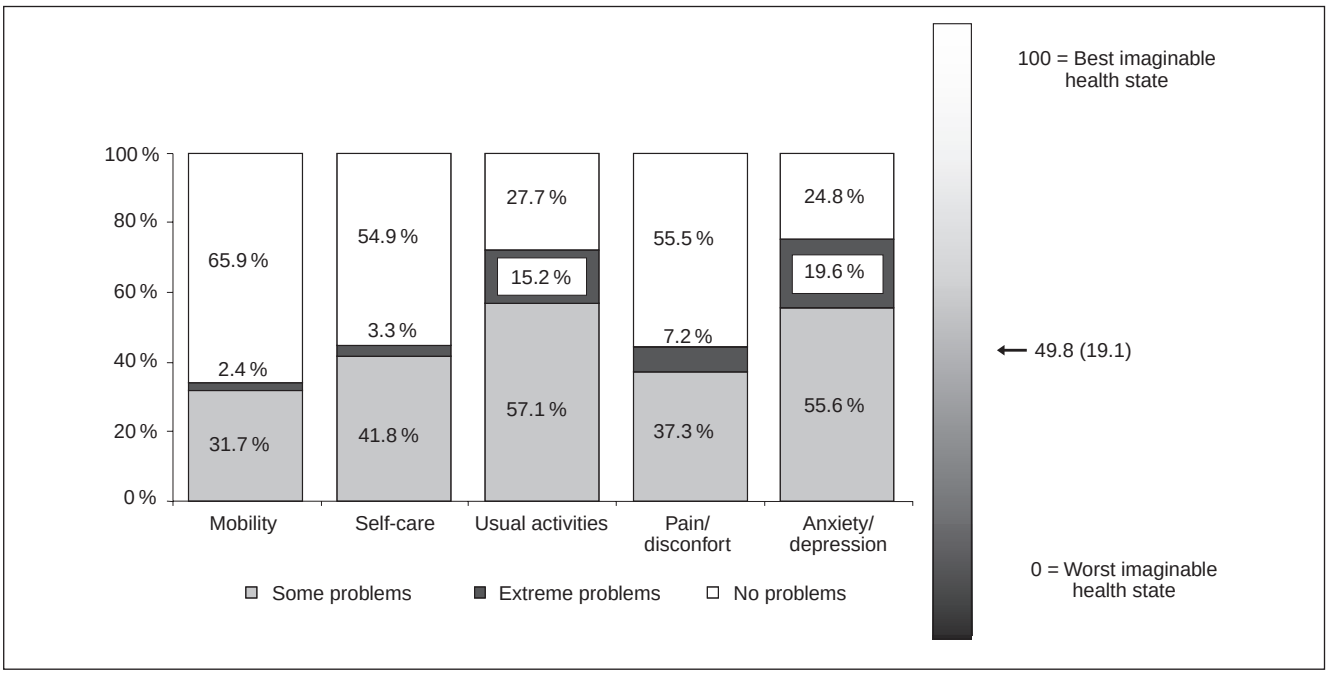

Figure 3. Baseline health-related quality of life (EuroQol and VAS) of the Spanish sample.

The most frequent reason for change in all groups was lack of effectiveness (especially with quetiapine: 80.9%) followed by intolerability (risperidone: 42.3%, and haloperidol: 40.3%) and patients request in the other two (olanzapine: 43.6%, and clozapine: 35.9%). The results obtained with quetiapine can be explained from the perspective that there could be a relationship between doses usually prescribed in the clinical practice and a poor clinical response. By other hand, both risperidone and the typical antipsychotics are limited in use because of the presence of side effects, mainly extrapyramidal symptoms. The fact that up to 43.6% of the patients with olanzapine expressed the desire to change seems to be not so clearly defined (in clozapine it could be related with the usual fixed hematological follow-up). Anyway, it does not seem to be related with tolerability concerns since only 13.3% of the patients included into this group expressed this last reason associated to the desire of change. Undoubtedly an additional analysis is needed to give an answer to this question.

Taking into account the sample characteristics (patients who require the beginning or the change of the antipsychotic treatment but still as outpatients), it is not so surprising that the mean global-CGI-SCH is 3.5 (SD: 0.9) «moderately or markedly ill» and that the negative symptoms are the predominant, with a negative CGI-SCH of 3.2 (1.2), although the scores of other subscales were not significantly different (positive CGI-SCH of 3.0 [1.3], cognitive CGI-SCH 2.8 [1.2], depressive CGI-SCH of 2.5 [1.2]). Up to 49.2% of the patients presented a global CGI-SCH > 4, i.e. half the sample were at least markedly ill at the study beginning.

The SOHO study sample had considerable functional impairment at baseline. Only 24.9% of patients were involved in a relationship at baseline, and 31.8% had no social activity in the 4 weeks prior to the baseline assessment. The proportion of patients in paid employment was only 16.2%.

The EuroQoL results have provided an important insight into the health status of the patients with schizophrenia included in the study. Although extreme problems with mobility and self-care were rarely reported, there was a high level of reported problems in performing usual activities and with anxiety/depression. The overall scores provided by the tariff and the visual analogue scale (VAS) indicate a severe self per-

TABLE 4. Health resources utilization of the Spanish sample

Resource	*N*	*%*	*Mean (SC)*	*Median (IQR)*
Inpatient in previous 6 months	690	34.2		
Admissions			1.9 (2.0)	1 (1-2)
Days			31.4 (30.7)	21 (12-40)
Day hospital in previous 6 months	458	22.7		
Days			42.2 (43.4)	30 (10-60)
Outpatient currently	1,943	96.2		
Visits			10.1 (15.2)	5 (3-9)

ception of health status, especially when compared with results provided for general population and other groups of patients[20]. Mean values for the tariff score, for example, went from 0.87 to 0.89 for a sample of the Spanish general population, while the same values went from 0.27 to 0.75 when administered to severe and chronic patients, respectively. The mean score for the patients with schizophrenia in this study was 0.6, positioning them below the score obtained by the sample of chronic patients reported by Badía[20].

CONCLUSION

We have presented results from the baseline assessment of the Spanish sample of SOHO study. SOHO is a three-year prospective study that will start producing valuable results about antipsychotic treatment for schizophrenia in Europe. Although, due to the observational characteristic of this study, there was no random assignment to the treatment groups, the baseline homogeneity assessed among all treatment groups will allow to consider further comparisons between olanzapine group and control group. These further analyses will concentrate on many other research questions, which include:

— Assessment of the predictors of antipsychotic treatment choice.
— Further exploration of the reasons behind the use of multiple antipsychotics for the treatment of out-patients with schizophrenia.
— Investigation of the differences in patterns of use of antipsychotics in European countries and the reasons behind these differences.

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