

Effectiveness of antipsychotic treatment for schizophrenia: Italian results of the pan-European Schizophrenia Outpatient Health Outcomes (SOHO) study after 12 months

Efficacia della terapia antipsicotica per la schizofrenia: i risultati italiani a 12 mesi dello studio pan-europeo SOHO (Schizophrenia Outpatient Health Outcomes)

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The SOHO study is funded by Eli Lilly and Company Limited, Windlesham, Surrey, UK

Key words

Antipsychotic agents • Italy • Schizophrenia • Treatment outcome • Outpatient

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Summary

Objectives

Schizophrenia therapy aims to control clinical symptoms and improve patient quality of life and functioning. The aim of this study was to present the 12-month outcomes associated with antipsychotic treatment of Italian patients participating in the Schizophrenia Outpatient Health Outcomes (SOHO) study. SOHO is a 3-year, prospective, observational study of the health outcomes associated with antipsychotic treatment in 10 European countries, with a special focus on olanzapine.

Methods

The study included over 10,000 patients who were initiating or changing their antipsychotic medication; 3,016 patients were enrolled in Italy. Data are presented for the 1,472 Italian patients who started antipsychotic monotherapy at baseline and maintained this treatment for 12 months (completers). Data are summarised by treatment cohort and multivariate analysis was used to compare each treatment cohort with the olanzapine cohort.

Results

A large proportion of completers responded to treatment (improvement in Clinical Global Impression-overall symptoms) during the 12 months, ranging from 53% in the depot typical cohort to 72% in the clozapine cohort (Fig. 3). The odds of responding to treatment were significantly greater with olanzapine than with risperidone or typical antipsychotics (oral or depot) (Table III). Likewise, patients receiving olanzapine were more likely to respond in terms of negative or depressive symptoms than patients receiving risperidone or typical antipsychotics, and more likely to respond in terms of cognitive symptoms than patients receiving typical antipsychotics (Table III). Clinical response to treatment was comparable between clozapine and olanzapine, but patients treated with clozapine were more likely to be socially inactive at 12 months. Patient quality of life improved in all treatment cohorts (measured using the EuroQol-5D visual analogue scale, EQ-5D VAS), but there was a significantly greater improvement in EQ-5D VAS with olanzapine than with risperidone or depot typical antipsychotics (Fig. 4). Patients receiving olanzapine have significantly less likelihood of having extrapyramidal symptoms at 12 months than patients in the risperidone, quetiapine or typical antipsychotic cohorts (Table IV), but had a significantly greater exposure to weight gain. Sexual adverse events remained a problem associated with all antipsychotics after 12 months of treatment, but were less likely to be present with olanzapine than with other atypical or typical antipsychotics (Table IV).

Conclusions

Italian outpatients with schizophrenia who maintain treatment with the same antipsychotic for 12 months in a naturalistic setting show clinical improvements that are accompanied by better quality of life and some improvements in social functioning. Clozapine and olanzapine appear to be associated with better outcomes than other antipsychotic agents.

Introduction

Randomised clinical trials (RCTs) have provided much of our current knowledge about the effects of antipsychotic drugs and are the evidence base for current guidelines and recommendations for the treatment of schizophrenia¹⁻⁴. Due to certain inherent design limitations, RCTs cannot fully reflect the use and impact of antipsychotic medications in real clinical practice. Most RCTs are of short duration⁵, involve selected samples of patients^{6,7}, focus on clinical outcomes instead of quality of life or social functioning⁸, and impose stringent treatment regimens that limit the generalisability of the results⁹⁻¹¹.

The results of observational studies can be considered to complement those of RCTs. Observational studies usually have higher external validity because samples are more representative of the daily practice population, whereas RCTs have higher internal validity due to their design accuracy and standardized procedures¹². In general, observational studies have other advantageous features, including longer follow-up periods, no limitations imposed on drug dosage or concomitant medication, and better representation of the complexities of clinical practice. However, many existing observational studies of the pharmacotherapy of schizophrenia have had limitations in size or scope, design, and statistical rigour to fully address the impact of antipsychotic drugs in real clinical practice¹³⁻¹⁷.

The aim of schizophrenia therapy is not only to control clinical symptoms, but also to improve the quality of life and functioning of patients. Recent data from observational and other studies indicate that symptom improvements correlate only weakly with improved patient functioning or quality of life^{18,19}. Thus, both clinical and functional outcomes should be assessed as they may be differentially affected according to the severity and type of schizophrenic symptoms and other factors, such as treatment emergent adverse events.

The European Schizophrenia Outpatient Health Outcomes (SOHO) study is the largest naturalistic study of antipsychotic drug treatment for schizophrenia ever conducted. It is a 3-year, prospective, observational study of the outcomes of antipsychotic treatment for schizophrenia in the outpatient setting in 10 European countries, including Italy. The SOHO study includes patients taking any antipsychotic drug, but has a specific focus on the atypical antipsychotic, olanzapine^{13,20}. Since a considerable proportion of the SOHO study population was from Italy (n = 3,016; 27.5%) and no other data is available on such a large number of Italian patients with schizophrenia, we have examined the 12-month outcomes associated with the continuous use of different antipsychotic treatments as monotherapy in the Italian patients taking part in the SOHO study.

Methods

STUDY SETTING AND DESIGN

The SOHO study was conducted in 10 European countries (Denmark, France, Germany, Greece, Ireland, Italy, The Netherlands, Portugal, Spain and the UK), but the results presented in this paper are for the Italian patient population only. Details of the study rationale, methods and recruitment have been described elsewhere¹³, together with the pan-European baseline findings and 6-month efficacy and tolerability results for the total study population²⁰⁻²². All Italian centres received administrative and ethics committee approval and all Italian patients gave written informed consent. A total of 10,972 patients were enrolled in the SOHO study. Of these patients, 3,016 were enrolled in Italy by 132 investigators, who were psychiatrists working mostly in public practices.

Participating psychiatrists were asked to include adult patients (≥ 18 years) who had initiated or changed antipsychotic medication for the treatment of schizophrenia in an outpatient setting or in a hospital setting when admission was planned for the initiation of antipsychotic medication and discharge planned within 2 weeks. Patients were included irrespective of the reason for the treatment change (e.g. lack of response, adverse events, etc.), and regardless of whether an antipsychotic drug was being initiated as a replacement for a previous medication, was an addition to existing treatment, or was being initiated for the first time or after a period of no treatment. All patient care was at the discretion of the participating psychiatrist; no instructions or recommendations for the provision of care or pharmacotherapy were included in the study protocol. The study was designed to provide two patient cohorts of approximately equal size: 1) patients who initiated therapy with or changed to olanzapine; and 2) patients who initiated therapy with, or changed to, a non-olanzapine antipsychotic. Stratified sampling was used to achieve approximately equal numbers in the olanzapine and non-olanzapine groups. Effort was made to avoid interference with clinical practice. Investigators were instructed to make treatment decisions before, and independently from, assessing patient suitability for inclusion in the study. A long recruitment period (1 September 2000 to 31 December 2001) was used and no minimum number of cases per investigator was required.

ASSESSMENT

Data collection occurred during visits that were part of the normal course of treatment. The normal practice outpatient visit at which patients were enrolled served as the baseline data collection visit. Post-baseline data collection was targeted for 3 months, 6 months, and then every 6 months up to 36 months.

For each data collection target, investigators were allowed to collect data within the interval 1 month prior to and after the target month. Patients who did not have data collected at one target point were not excluded from subsequent data collection.

Several outcomes were assessed in the study, including clinical severity, Health-Related Quality of Life (HRQoL), and social functioning. Clinical severity was assessed using the physician-rated Clinical Global Impression-Schizophrenia scale (CGI-SCH)²³, which was based on the Clinical Global Impression (CGI)²⁴. With the CGI-SCH, physicians rate the severity of a patient's symptoms (positive, negative, cognitive, depressive and overall) during the previous week using a scale ranging from 1 (normal, not ill) to 7 (among the most severely ill).

HRQoL was assessed using the EuroQol-5 Dimensions (EQ-5D), a patient self-rated, generic HRQoL instrument composed of two parts: five questions that assess quality of life in different domains (mobility, self-care, usual activities, pain, and anxiety/depression); and a Visual Analogue Scale (EQ-5D VAS)²⁵, where patients self-rate their overall health on a scale of 0-100, with 0 representing the lowest possible health and 100 the best possible health.

Social functioning was assessed using single-item questions that analysed whether patients had one or more social activities in the previous 4 weeks (patient socially active), had paid employment, a relationship with a spouse or partner, or were exhibiting verbal or physical hostility or aggressive behaviours. Drug tolerability (extrapyramidal symptoms [EPS], sexual dysfunction, weight changes) was assessed at each visit.

DEFINITION OF RESPONSE

Response, in terms of clinical symptoms, was defined as a 2-point decrease in the CGI-severity rating from baseline to follow-up when the baseline rating was 5-7 points, or a 1-point decrease when the baseline rating was 2-4 points. This definition of response was delineated without knowledge of the study results by agreement of all members of the SOHO advisory board.

STATISTICAL ANALYSIS

The analyses presented in this paper are for the Italian patients who started antipsychotic monotherapy at the baseline visit and maintained this treatment for 12 months (completers). Data were analysed by treatment cohort, defined according to the antipsychotic started at baseline. The following treatment cohorts were analysed: olanzapine, risperidone, quetiapine, oral typical, clozapine, and depot typical. Patients starting two or more antipsychotics at the baseline visit ($n = 98$) and patients taking amisulpride ($n = 2$) were excluded from the analysis.

Bivariate comparisons of the outcomes at 12 months for each treatment cohort were performed. In addition, regression models that adjusted for baseline differences between the cohorts were fitted. The medication reference category for the regression models was the olanzapine cohort (the group with the largest number of patients). For the analysis of whether the patients responded to treatment according to the different CGI-SCH dimensions, a generalized estimating equation (GEE) model with a logit link and an unstructured covariance variance was used. The 3-, 6- and 12-month data were included in the model. The baseline values of the following covariates were included in the model: antipsychotic initiated at baseline (cohort); study visit; age; gender; age at first treatment contact for schizophrenia; body mass index (BMI); never treated with antipsychotics before inclusion in SOHO; antipsychotic treatment in the 6 months prior to enrolment (dichotomous variables for typical antipsychotics, clozapine, olanzapine, risperidone, other atypical antipsychotics or no antipsychotics). The same regression model was used for the analysis of social activities, EPS, sexual adverse events and hostility.

Analysis of variance (ANOVA) was used to model the data for improvement in EQ-5D VAS. The covariates included in the model were the same as in the GEE model. It should be noted that only approximately 80% of the sample were included in the multivariate models, due to missing values in the covariates. Since the observational nature of the SOHO study can lead to multiple between-cohort differences, we report the adjusted odds ratios (OR) and 95% confidence intervals (95% CIs) from the models. ANOVA was also used for weight change and the results are presented as adjusted mean change and 95% CIs.

Results

PATIENT CHARACTERISTICS

Of the 3,016 Italian patients enrolled in the SOHO study, 2,110 were taking monotherapy at the beginning of the study and had sufficient information for the analysis. Of these patients, 1,472 (70%) completed 12-months treatment with the same antipsychotic monotherapy (completers) and 636 (30%) patients interrupted or changed therapy during this period (non-completers). Two patients prescribed amisulpride monotherapy at baseline have been excluded from the analysis.

The baseline socio-demographic and clinical characteristics of the completers and non-completers are summarised in Table I. There were no relevant dif-

Table I. Baseline socio-demographic and clinical characteristics of completers and non-completers. *Caratteristiche socio-demografiche e cliniche basali dei pazienti che hanno completato lo studio vs. pazienti che non lo hanno completato.*

	Completers (n = 1472)	Non-completers (n = 636)
Age at baseline, y	40.2 (12.8)	40.5 (12.2)
Male, n (%)	840 (57)	387 (61)
Age at first contact, y	27.4 (9.6)	27.0 (9.1)
BMI, kg/m ²	25.9 (4.7)	26.6 (5.0)
CGI-overall	4.4 (1.0)	4.5 (1.0)
Independent housing, n (%)	513 (35)	223 (35)
Paid employment, n (%)	244 (17)	99 (16)
Inpatient admission in 6 months before baseline, n (%)	399 (31)	217 (38)
Suicide attempt, n (%)	36 (3)	20 (4)
On antipsychotic medication at baseline, n (%)	992 (67)	526 (82)

Data are given as mean (SD) unless indicated otherwise.

ferences in these baseline characteristics between the completers and non-completers.

The medication prescribed at baseline for the patients who stayed on the same antipsychotic drug as monotherapy for 12 months (completers) is summarised in Figure 1. Fifty four per cent of completers received olanzapine monotherapy for 12 months, which reflects the study design of enrolling approximately 50% of patients to olanzapine and 50% to non-olanzapine therapy. A high percentage of Italian patients continued to receive at 12 months the antipsychotic drug they initiated as monotherapy at baseline, although it varied by antipsychotic, ranging from 48% with quetiapine to 78% with clozapine (Fig. 2). The median doses of olanzapine and risperidone prescribed at baseline remained unchanged over 12 months of treatment, whereas there was noticeable dose titration with quetiapine and clozapine in the first 3 months (Table II). The doses of oral and

depot typical antipsychotics are not given because many different preparations were used and chlorpromazine equivalents have not been calculated.

Among the non-completers, between 44% of patients in the oral typical antipsychotic cohort and 72% of patients in the quetiapine cohort had one change in therapy over 12 months, whereas 28-56% of patients had two or more changes in therapy over the 12-month period.

CLINICAL EFFECTIVENESS

A large proportion of completers in each antipsychotic cohort responded to treatment (improvement in CGI-overall symptoms) during the 12 months of treatment, ranging from 53% in the depot typical cohort to 72% in the clozapine cohort (Fig. 3). Among the non-completers, the proportion of responders at 12 months was 53% (one change in therapy) and 48% (two or more changes in therapy).

The multivariate analysis comparing completers in the olanzapine cohort with completers in the other cohorts showed a significantly higher likelihood of

Fig. 1. Medication prescribed at the baseline visit in completers (patients completing 12 months treatment with the same antipsychotic monotherapy prescribed at baseline), n = 1472. *Farmaco prescritto al basale nei pazienti che hanno completato i 12 mesi di studio, utilizzando lo stesso antipsicotico (n = 1472).*

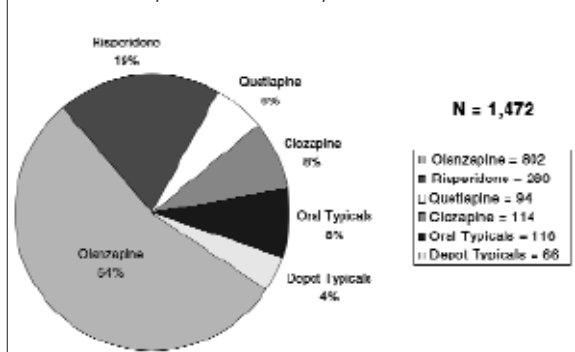


Fig. 2. Proportion of patients continuing initial antipsychotic medication by treatment group. *Percentuale di pazienti che hanno continuato ad assumere lo stesso antipsicotico utilizzato all'inizio dello studio, per gruppo di trattamento.*

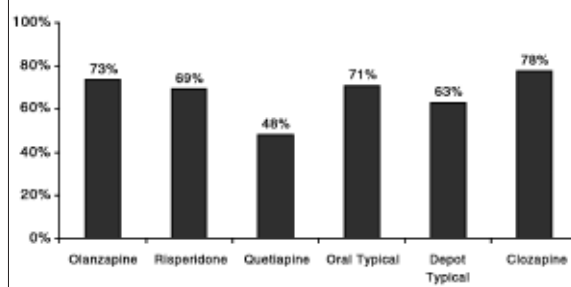
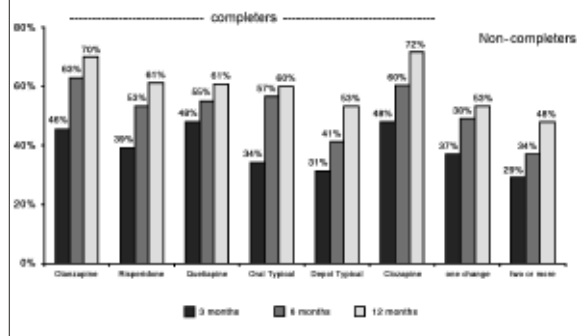


Table II. Antipsychotic dosages prescribed at baseline and during 12 months of treatment. *Dosaggi prescritti dei diversi antipsicotici al baseline e dopo 12 mesi di terapia.*

	Mean (SD) and median dose (mg)							
	n.	Baseline	n.	3 months	n.	6 months	n.	12 months
Olanzapine	787	10.9 (5.1); 10	784	12.3 (5.6); 10	782	12.4 (5.8); 10	775	12.5 (6.0); 10
Risperidone	273	3.8 (2.0); 4	272	4.2 (2.2); 4	269	4.2 (2.3); 4	268	4.2 (2.3); 4
Quetiapine	93	258 (188); 200	93	364 (188); 400	93	375 (208); 300	91	378 (215); 400
Clozapine	114	136 (106); 100	112	204 (122); 200	113	224 (124); 200	110	232 (121); 225

SD = Standard deviation.

Note: mean and median doses of oral and depot typical antipsychotics are not given because many different preparations were used and chlorpromazine equivalents have not been calculated.

Fig. 3. Percentage of patients responding to treatment (improvement in CGI-overall symptoms) by treatment group in completers and non-completers. *Percentuale di pazienti che hanno risposto alla terapia (miglioramento della scala CGI – sintomi complessivi) per gruppo di trattamento, sia per i pazienti “completers” che per i “non-completers”.*

responding in terms of improvement in CGI-overall symptoms with olanzapine compared with risperidone and oral typical or depot typical antipsychotics (Table III). For CGI-positive symptoms, the odds ratios and 95% confidence intervals showed no significant difference between treatment cohorts in the likelihood of response at 12 months. For CGI-negative symptoms, patients in the olanzapine cohort were more likely to respond than patients receiving risperidone, quetiapine and oral typical or depot typical antipsychotics. Olanzapine treated patients were also significantly more likely to respond at 12 months in terms of CGI-depressive symptoms than patients receiving risperidone and oral typical or depot typical antipsychotics. Likewise, olanzapine-

treated patients were significantly more likely to respond in terms of improvements in cognitive symptoms (CGI-cognitive) than patients treated with oral typical or depot typical antipsychotics.

SOCIAL ACTIVITIES

At baseline, the percentage of completers with no social activities ranged from 31% in the risperidone cohort to 45% in the depot typical cohort. All treatment cohorts showed a decrease over 12 months in the proportion of patients who had no social activities. At 12 months, the proportion of patients with no social activities was higher in the clozapine (23%) and depot typical (26%) cohorts compared with the risperidone (13%), olanzapine (14%), quetiapine (16%) and oral typical (16%) cohorts.

The multivariate analysis showed that patients in the clozapine cohort had a significantly greater likelihood of not being socially active at 12 months compared to patients treated with olanzapine (OR 2.14, 95% CIs 1.13, 4.09).

QUALITY OF LIFE

Patient quality of life improved during antipsychotic treatment for 12 months. The mean EQ-5D VAS total score increased from baseline to 12-months in all treatment cohorts (Fig. 4), with the mean change from baseline ranging from 14 in both the oral and depot typical cohorts to 23 and 25 in the olanzapine and clozapine cohorts, respectively.

Multivariate analysis demonstrated that there was a significantly greater improvement in EQ-5D VAS with olanzapine compared with risperidone (adjusted mean change 4.37, 95% CIs 1.78, 6.97) and oral typical (adjusted mean change 8.33, 95% CIs 4.64, 12.01) antipsychotics.

Table III. Multivariate analysis of odds ratios and 95% confidence intervals of clinical response at 12 months in antipsychotic cohorts compared with the olanzapine cohort. *Analisi multivariate della odds-ratio ed intervalli di confidenza (95%), della risposta clinica a 12 mesi tra la coorte di pazienti che utilizzava olanzapina e le coorti di pazienti che utilizzavano gli altri antipsicotici.*

CGI	Odds ratio (95% confidence intervals)				
	Risperidone	Quetiapine	Clozapine	Oral typical	Depot typical
Overall symptoms	1.42 (1.03, 1.97)	1.47 (0.9, 2.39)	0.97 (0.59, 1.58)	1.69 (1.07, 2.66)	2.33 (1.31, 4.13)
Positive symptoms	1.00 (0.70, 1.43)	1.25 (0.75, 2.11)	1.02 (0.62, 1.68)	1.39 (0.85, 2.28)	1.61 (0.88, 2.93)
Negative symptoms	1.39 (1.00, 1.93)	1.78 (1.07, 2.94)	1.01 (0.62, 1.63)	1.81 (1.14, 2.87)	2.16 (1.21, 3.84)
Depressive symptoms	1.51 (1.08, 2.11)	1.37 (0.82, 2.28)	0.93 (0.57, 1.54)	2.64 (1.64, 4.23)	3.04 (1.64, 5.64)
Cognitive symptoms	1.31 (0.94, 1.83)	1.47 (0.89, 2.45)	0.63 (0.38, 1.05)	1.73 (1.09, 2.75)	2.27 (1.22, 4.21)

Response defined as a 2-point decrease in the CGI score (scale 1 to 7) when baseline score is between 5 and 7 or 1-point decrease if baseline score is between 2 and 4.

An odds ratio greater than 1 indicates the odds of responding are greater in the olanzapine cohort

CGI = Clinical Global Impression.

TOLERABILITY

Among the completers, the proportion of patients with EPS at 12 months was higher in the depot typical (32%) and oral typical (30%) antipsychotic cohorts compared with patients taking risperidone (16%), quetiapine (10%), clozapine (9%) or olanzapine (8%). Multivariate analysis showed that patients in the olanzapine cohort has significantly less observation of having EPS at 12 months than patients in the risperidone, quetiapine and oral typical or depot typical antipsychotic cohorts (Table IV).

The proportion of patients requiring anticholinergics at 12 months was reduced to 4-11% in the clozapine, olanzapine, quetiapine and risperidone groups, but remained high in the oral typical (35%) and depot typical (32%) antipsychotic groups.

In each treatment cohort, there was an increase in mean weight during the 12 months of treatment. Mean (SD) weight gain from baseline to 12 months in each of the treatment cohorts was as follows: olanzapine 3.03 (5.67) kg, clozapine 2.03 (5.74) kg,

risperidone 1.89 (4.51) kg, oral typical 1.38 (4.78) kg, quetiapine 1.07 (6.19) kg, and depot typical 0.61 (5.45) kg. Multivariate analysis showed that there was significantly greater weight gain in the olanzapine cohort compared with the risperidone (adjusted mean change 1.29 kg, 95% CIs 0.48, 2.09), quetiapine (adjusted mean change 1.77 kg, 95% CIs 0.54, 2.99) and oral typical (adjusted mean change 2.00 kg, 95% CIs 0.85, 3.15) and depot typical (adjusted mean change 1.83 kg, 95% CIs 0.35, 3.3) antipsychotic cohorts.

The proportion of patients with hostile behaviour fell from baseline levels which ranged from 21% (risperidone) and 35% (clozapine), to between 3% (olanzapine) and 11% (depot typical) at 12 months. Multivariate analysis revealed that the odds of being hostile at 12 months was significantly greater in the oral typical and depot typical cohorts compared with the olanzapine cohort (Table IV).

SEXUAL ADVERSE EVENTSS

The proportion of patients experiencing 'loss of libido' decreased from baseline to 12 months in all treatment groups. At 12 months, loss of libido was present in a high percentage of all completers (30.8%), ranging from 25.3% for the quetiapine cohort to 38.1% for the depot typical antipsychotic cohort. Similarly, the percentage of patients with 'impotence/sexual dysfunction' decreased in all treatment groups from baseline to 12 months and, at 12 months, was present in 21.4% of patients ranging from 17.1% with quetiapine to 32.0% with clozapine. Amenorrhoea was present in 16.9% of patients at 12 months, ranging from 10.3% with quetiapine to 27.2% with risperidone. A low proportion of patients had adverse events such as gynaecomastia (2.3%) and galactorrhoea (0.3%) at 12 months of treatment.

Fig. 4. Mean EQ-5D VAS scores over 12 months by treatment cohort. *Punteggi medi della scala EQ-5D VAS nel corso dei 12 mesi, per coorte di terapia.*

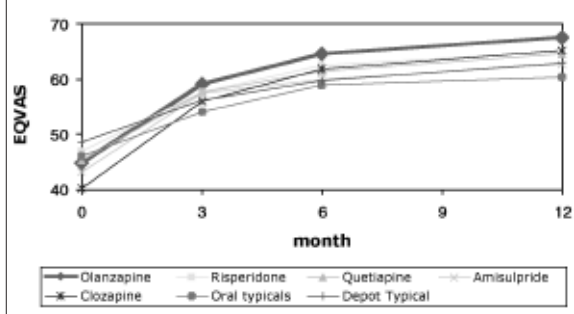


Table IV. Multivariate analysis of adjusted odds ratios (OR) and 95% confidence intervals of adverse events at 12 months in antipsychotic cohorts compared with the olanzapine cohort. *Analisi multivariate della odds-ratio (OR) normalizzate ed intervalli di confidenza (95%), dell'incidenza di eventi avversi a 12 mesi tra la coorte di pazienti che utilizzava olanzapina e le coorti di pazienti che utilizzavano gli altri antipsicotici.*

	Olanzapine	Risperidone	Quetiapine	Clozapine	Oral typical	Depot typical
Extrapyramidal symptoms	1	3.33 (1.98, 5.59)	2.43 (1.08, 5.49)	1.11 (0.49, 2.55)	9.13 (4.79, 17.38)	6.92 (3.53, 13.56)
Hostility	1	1.12 (0.61, 2.07)	2.31 (1.01, 5.26)	1.39 (0.67, 2.90)	2.43 (1.15, 5.09)	2.90 (1.21, 6.95)
<i>Sexual dysfunctions</i>						
Loss of libido	1	1.96 (1.24, 3.09)	1.42 (0.69, 2.92)	1.31 (0.72, 2.37)	1.87 (0.98, 3.59)	1.80 (0.84, 3.88)
Impotence/sexual function	1	1.01 (0.56, 1.82)	1.11 (0.45, 2.74)	1.36 (0.70, 2.64)	1.46 (0.62, 3.43)	0.83 (0.32, 2.18)
Amenorrhoea	1	3.30 (1.43, 7.61)	0.67 (0.16, 2.72)	1.41 (0.39, 5.07)	0.69 (0.23, 2.09)	1.26 (0.42, 3.74)
Gynaecomastia	1	10.76 (2.67, 43.38)	1.94 (0.07, 51.42)	0.81 (0.13, 5.06)	2.22 (0.51, 9.60)	2.52 (0.29, 21.86)

OR > 1 indicates odds of having side-effects are greater than in the olanzapine cohort.

The adjusted ORs and 95% CIs from the logistic regression models of adverse events at 12 months post-baseline for each of the treatment groups compared to the olanzapine group are summarised in Table IV.

Discussion

The SOHO study is the largest prospective observational investigation of the long-term use and outcomes associated with antipsychotic drugs in schizophrenia. This analysis of the Italian outpatients found that patients who required initiation or a change in their antipsychotic for clinical reasons and completed 12 months of treatment with same antipsychotic monotherapy, showed a marked improvement in symptoms that translated into improvements in their HRQoL and in social activities.

An important finding of this study was that a large proportion of patients (70%) who started treatment with one antipsychotic drug were still on the same drug at the end of 12 months (completers). For patients prescribed atypical antipsychotics, the proportion of completers ranged from 48% with quetiapine to 78% with clozapine. These data are consistent with recent literature, where the percentage of patients persisting with atypical antipsychotics was 50-60% after one year of treatment²⁶.

There are both advantages and limitations of examining the data for patients who are completers. One advantage of analysing data from completers is that it provides useful information on the long-term effects of continuing on the same medication; it provides information about adverse events and about quality of life changes for patients remaining on the same antipsychotic for 12 months. However, an important limitation of this approach is that only provides information about patients who respond and/or tolerate their prescribed treatment. Examination of the results

for non-completers, who switch to another antipsychotic and/or take additional antipsychotics, will also provide useful information.

Previous studies have shown that all antipsychotic drugs are effective against positive symptoms, and that the atypical antipsychotics have greater clinical activity against negative and depressive symptoms than typical antipsychotics (oral or depot)²⁷. Clozapine and olanzapine appear to have similar efficacy in improving negative symptoms, and are more effective than risperidone and quetiapine, which are equally effective^{8, 28, 29}. Our results on completers confirm these findings; clozapine and olanzapine were the most effective antipsychotics, and olanzapine was significantly more effective than typical antipsychotics (oral or depot) against negative, depressive and cognitive symptoms.

Among the completers, the median daily doses of olanzapine (10 mg) and risperidone (4 mg) during the 12 months of treatment were similar to those reported in clinical trials and in line with clinical experience for the maintenance treatment of schizophrenia³⁰⁻³². Although the median daily dose of clozapine at 12 months (200 mg) was relatively low compared to that recommended by the American Psychiatric Association guidelines (150-600 mg)³³, it was effective against all clinical outcomes assessed in the study. In the present study, quetiapine was prescribed at a median daily dose of 400 mg at the end of the 12 months, which is lower than that used in other studies^{34, 35}. A possible explanation for this is that quetiapine had just become available in Europe at the time patients were included in the study, therefore, the participating psychiatrists were less familiar with using this drug.

HRQoL (EQ-5D VAS) was improved in all treatment cohorts at 12 months, but was significantly greater in the olanzapine cohort compared with the risperidone and depot typical cohorts. It has been suggested that

the optimal treatment of schizophrenia involves not only treating positive symptoms, but also addressing other symptoms, such as depression, cognition and social functioning, which affect patient quality of life³⁶. Our results confirm that the high clinical efficacy of clozapine and olanzapine (negative symptoms) and clozapine, olanzapine, quetiapine and risperidone (cognitive symptoms) is accompanied by improvements in patient social activities and quality of life. Patients treated with olanzapine had a significantly lower observation of having EPS at 12 months compared with patients receiving risperidone or typical antipsychotics. This supports previous reports, including a systematic meta-analysis of RCTs³⁷, which found that olanzapine treatment had a more favourable EPS than treatment with typical antipsychotics and may have a more favourable EPS than treatment other atypicals. In addition, in a recent study of neurologic soft signs in schizophrenic patients, those treated with risperidone had higher observations of EPS symptoms compared with patients treated with other atypical antipsychotics³⁸. A surprising finding of our study was that quetiapine treatment was observed to have more EPS than olanzapine. Quetiapine treatment is generally considered to have a more favourable EPS profile than treatment with olanzapine³⁹. We found that approximately one-third of patients undergoing therapy with typical antipsychotics continued to use anticholinergic drugs at 12 months, while there was a much lower rate of anticholinergic use among patients treated with atypical antipsychotics (4-11%). The reduction in anticholinergic use among patients receiving atypicals may be associated with the reduction in EPS in these patients. Changes in weight are an important concern for patients treated with antipsychotics and may influence their adherence with medication⁴⁰. Notably, we found that olanzapine was associated with significantly more weight gain than risperidone, quetiapine and typical antipsychotics. Our results underline the importance of weight management when a new antipsychotic is used. Most studies that assess weight change are short-term and report mean weight changes, which can obscure the marked individual variation in weight change that occurs during an-

tip psychotic treatment⁴¹. In several long-term naturalistic studies (> 6 months), the mean weight gain was less marked than that reported in RCTs of shorter or comparable duration⁴². As the SOHO study will continue for 3 years, the long-term association between antipsychotic treatment and body weight will be determined.

Sexual adverse events are an under-addressed problem associated with all antipsychotic therapies. Reduction/loss of sexual interest, impotence and amenorrhoea are the most common sexual adverse events experienced by patients during antipsychotic therapy. It is not surprising that the highest rate of loss of libido occurred among patients using depot neuroleptics because, traditionally, these agents have been used to treat the most seriously ill patients, those with poor compliance, with a long history of illness and often those receiving multiple treatments^{43 44}. Clozapine was associated with the highest rate of impotence/sexual dysfunction at 12 months (32%). This may be related to its anticholinergic effects, which can include delayed ejaculation (or retrograde ejaculation)⁴⁴.

We found a significantly increased observation of amenorrhoea among women treated with risperidone compared with those receiving olanzapine. This is consistent with previous reports that therapeutic doses of atypical antipsychotics differ with regard to their effect on prolactin secretion; risperidone was frequently associated with hyperprolactinaemia and related symptoms, whereas the occurrence of prolactin elevation and related symptoms was modest in patients receiving olanzapine and non-existent in those receiving clozapine⁴⁵.

The 12-month results of the SOHO study presented here show that Italian patients who require an antipsychotic treatment change for clinical reasons show significant clinical improvements that translate into better self-rated quality of life and some improvements in social functioning. Clozapine and olanzapine treatment seem to be associated with slightly better outcomes than other antipsychotic agents. As these results belong to a study closer to normal clinical practice than RCTs, they may better reflect the daily psychiatric approach to treating outpatients with schizophrenia in Italy.

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Acknowledgements

The Italian SOHO study group: P. Pancheri, F. Asioli, R. Brugnoli, L. Ferranini, V. Gatti, A. Giannelli, A. Laddomada, C. Munizza, E. Pirfo, M. Raja, F. Ramacciotti, V.P. Rapisarda, P. Serra. The authors acknowledge the contribution of the SOHO advisory board: Jean-Pierre Lepine, Hôpital Fernand Widal, Paris, France; Isabelle Gasquet, Hôpital Paul Brousse, Villejuif, France; Dieter Naber, Universitätskrankenhaus-Eppendorf, Klinik für Psychiatrie und Psychotherapie, Hamburg, Germany; C.J. Slooff, Psychosencluster GGX N-Drenthe, Kenniscentrum Scizofrenie, R.A. Assen, The Netherlands; Jordi Alonso, Health Services Research Unit, Institut Municipal d'Investigacio Medica, University of Barcelona, Barcelona, Spain; Josep Maria Haro, Research and Development Unit, Sant Joan de Déu-SSM, Sant Boi, Barcelona, Spain; Tim Croudace, Department of Psychiatry, Addenbrooke's Hospital, Cambridge, UK; Peter B. Jones, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; Martin Knapp, London School of Economics, Centre for the Economics of Mental Health, Institute of Psychiatry, London, UK. Deirdre Elmhirst, PhD, assisted in the editorial development of the manuscript.