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Efficacy of antipsychotic treatment in schizophrenia: results after 24 months in Italian patients in the Schizophrenia Outpatient Health Outcomes (SOHO) study

Efficacia della terapia antipsicotica per la schizofrenia: risultati a 24 mesi dello studio SOHO (Schizophrenia Outpatient Health Outcomes) in Italia

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Key words

Antipsychotic agents • Italy • Schizophrenia • Treatment outcome • Outpatient

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Summary

Objectives

Aim of the present study was to examine the outcomes associated with antipsychotic treatment over a 24-month timeframe for Italian patients taking part in the Schizophrenia Outpatient Health Outcomes (SOHO) study.

Methods

SOHO is a prospective, observational study of the treatment of schizophrenia in over 10,000 patients in 10 European countries; 3,016 patients were enrolled in Italy. Data were collected at 6-month intervals. Given the complexity of the data, which include medication changes during follow-up, novel statistical methods have been applied, which include epoch analysis. In epoch analysis, patients are considered to have a new treatment episode when they change medication. Patients who switched antipsychotic treatment at 6, 12 or 18 months had their new treatment considered as a new baseline observation. Patients were then classified as having continuous antipsychotic treatment for 6, 12, 18 or 24 months. The following treatment groups were analysed: olanzapine, risperidone, quetiapine, clozapine, oral typicals and depot typicals. Multivariate analysis, adjusting for baseline covariates, examined treatment effects on various outcomes measures: clinical symptom severity (Clinical Global Impression-Schizophrenia Scale, CGI-overall), quality of life (EuroQol-5 dimensions visual analogue scale, EQ-VAS), social functioning (social activities, paid employment) and tolerability (incidence of extra-pyramidal symptoms [EPS] and weight change). Each treatment group was compared with the olanzapine group.

Results

A large number of patients (2,533) continued treatment for 24 months with the antipsychotic started at baseline. The CGI-overall score improved from baseline after continuous treatment for 6, 12, 18 and 24 months in all treatment groups (Fig. 2). Compared with olanzapine, there was significantly less improvement in the CGI-overall score for the other antipsychotic groups, except clozapine. Likewise, quality of life improved in all treatment groups in all epochs, and there was a significantly greater improvement in EQ-VAS with olanzapine compared with risperidone and oral typicals (Fig. 3). Social functioning also improved in all treatment groups, but more patients had social activities in the olanzapine group than in the clozapine group (after 6, 12 and 18 months continuous treatment) or typical antipsychotic groups (oral typical: after 6 and 12 months; depot typical: after 6 months continuous treatment) (Tab. V). Olanzapine, clozapine and quetiapine were associated with less EPS after treatment in all four epochs (Tab. VI). Olanzapine and clozapine were associated with higher average weight gain (Fig. 4).

Conclusions

Italian outpatients with schizophrenia in a naturalistic setting show improvements in clinical symptoms, quality of life and social functioning. Clozapine and olanzapine are associated with better outcomes despite weight gain observed more often than with other antipsychotics.

Introduction

Current guidelines and recommendations for the treatment of schizophrenia [1-5] are based largely on the evidence provided by randomised clinical trials (RCTs). While RCTs can demonstrate the efficacy of antipsychotic drugs, they are usually conducted in carefully selected samples of patients, are short-term and are performed under rigorously controlled conditions [6-12]. Thus, by their very design, RCTs do not reflect the full impact of schizophrenia and have a limited generalisability to patients in real-life clinical practice. Observational studies are intended to more closely reflect everyday clinical practice and can provide useful information on the real-life effectiveness of antipsychotic agents [13].

In schizophrenia, long-term treatment with antipsychotic agents is necessary. In everyday clinical practice and in observational studies, patients with schizophrenia may be prescribed more than one antipsychotic drug and frequently switch medication [14-16]. This can create difficulties when analysing the effects of treatment on outcomes of interest in observational studies. New methods of analysis, epoch analysis, have been developed to take into account medication changes when analysing treatment outcomes [17].

The European Schizophrenia Outpatient Health Outcomes (SOHO) study is a large, prospective, observational study on the outcomes of antipsychotic treatment for schizophrenia in the naturalistic outpatient setting in 10 European countries, including Italy [18 19]. The SOHO study included over 10,000 patients taking any antipsychotic drug. As no instructions regarding patient treatment were included in the study protocol, any patient was treated by the psychiatrist in the most appropriate manner, independently of study participation; as a consequence, many patients switched treatment during the course of the study. We previously reported the effectiveness of various antipsychotic drugs in a subgroup of 1,472 Italian patients in the SOHO study who completed 12 months of antipsychotic mono-therapy [20]. Aim of the present report is to describe the use of the epoch analysis to examine the efficacy and tolerability of continuous treatment with different antipsychotic medications as mono-therapy over a follow-up period of 24 months.

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 report refer only to the Italian patient population. Details of the study rationale, methods and recruitment have been described elsewhere [18], together with the pan-European baseline, 6-month, 12-month, and 3-year findings for the total study population [21-23]. 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, namely, 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. Patients were included irrespective of the reason for the treatment change (e.g. lack of response, side-effects, 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, ensuring the patient received the most appropriate therapy according to the judgement of the psychiatrist.

Since the study focused on the comparison of olanzapine with the other antipsychotic drugs, it 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. Every effort was made to avoid interference with clinical practice. Investigators were instructed to make treatment decisions before, and independently of, assessment of 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 was collected 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 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, depending on usual visit schedules. 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) [24], which was based on the Clinical Global Impression (CGI) [25]. With the CGI-SCH, physicians rate the severity of a patient's symptoms (positive, negative, cognitive, depressive and overall) during the day of assessment using a scale ranging from 1 (normal, not ill) to 7 (among the most severely ill).

HRQoL was assessed using the Italian version of the EuroQol-5 Dimensions (EQ-5D), a patient self-rated, generic HRQoL instrument composed of two parts: five questions that assess QoL in different domains (mobility, self-care, usual activities, pain, and anxiety/depression); and a Visual Analogue Scale (EQ-5D VAS) [26], 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 behaviour. Drug tolerability (EPS, sexual dysfunction, weight changes) was assessed at each visit.

Statistical analysis

The analyses presented in this paper are for all Italian patients with eligible data who were enrolled in SOHO and were at least observed at 6 months post-baseline.

The analysis is divided into two parts. First, we analysed the percentage of patients discontinuing the medication started at the baseline visit, until 24 months for those patients who completed the two-year follow-up. A logistic regression model was used to analyse medication differences in treatment maintenance, adjusting by baseline differences among medication cohorts.

Second, to analyse the outcomes associated with the different medication treatments, an epoch analysis approach was used. Patients' information was included in the epoch analysis until they had a missing visit. In those patients, the information prior to that visit was analysed. Epoch analysis is a new method of analysis that can be used when patients change medication during follow-up [17]. In this analysis, an episode of treatment is defined as the time the patient takes the same medication. When a patient changes medication, a new treatment episode is defined. Outcomes that occur between two visits are attributed to the medication taken between those two visits (medication taken upon presentation to the visit of the end of the period). The longitudinal analysis is then a series of conditional models (epochs) based on length of treatment. All patients are included in the first model (baseline to 6 months), the second model only considers patients who remain on the same treatment up to 12 months, the third model includes patients who remain on the same treatment up to 18 months, and so on. A major advantage of this method is that it allows all patient data to be used.

A patient who changed treatment could contribute more than one episode per epoch, with the repeated episode due to assignment to a different treatment group. For example, if a patient changed treatment at 6 months, he/she will start a new episode and the observation at the time of starting the new treatment was considered as a new baseline observation. Thus, each epoch provides information on treatment effects during the respective time period. Treatment change was defined as stopping the antipsychotic medication and/or adding a new antipsychotic.

In the analysis of medication outcomes, the following treatment groups were used: olanzapine, risperidone, quetiapine, clozapine, oral typicals and depot typicals. Only those patients taking antipsychotic monotherapy were included in the analysis; patients taking two or more antipsychotics were excluded from the analysis.

The following outcome measures were analysed: effectiveness (change in CGI-overall score), QoL (change in EQ-VAS score), social functioning (social activity, paid employment) and tolerability (EPS, change in weight). Multivariate analysis was performed to examine the effect of different treatments on the selected outcome measures for each of the four epochs. For each outcome measure, olanzapine was compared with the other antipsychotic medications. Odds ratios (ORs) for binary outcomes and mean estimates for continuous outcomes were adjusted for baseline covariates and presented together with 95% confidence intervals and level of significance. Given that the same patient could contribute to more than one observation, Generalised Estimation Equation (GEE) regressions [27] were used for the binary outcomes and linear mixed models for the continuous outcomes. The values of the OR of the logistic models represent the comparison of the response rate of the patients taking that medication during the epoch period compared with olanzapine. The values of the coefficients in the regression models represent the comparison of the values of the outcome variable of the patients taking that medication during the epoch period compared with olanzapine.

The baseline covariates included in the multivariate models were: age, sex, age at first treatment contact for schizophrenia, body mass index (BMI), involved in a relationship, independent housing, paid employment, social activity, never treated with antipsychotics, antipsychotic treatment in the 6 months prior to present treatment episode (oral typicals, depot typicals, clozapine, olanzapine, risperidone, other

atypical), receiving a concomitant prescription (anticholinergics, anti-depressants, anxiolytics, mood stabiliser), CGI (positive, negative, depressive, cognitive and overall symptoms), EPS, tardive dyskinesia (TD), loss of libido, gynaecomastia, galactorrhoea, amenorrhoea, impotence/sexual dysfunction, drug treatment compliance, current substance dependency, current alcohol dependency, hostility and EQ-VAS. In addition, the baseline value of the outcome measure was included as a covariate and the treatment group was added to the model.

Results

Study population

Of the 3,016 Italian patients enrolled in the SOHO study, there were 2,726 patient treatment episodes in the first epoch in which patients were treated with antipsychotic monotherapy (6 months of continuous treatment), 2,057 in the second epoch (12 months of continuous treatment), 1,629 in the third epoch (18 months of continuous treatment) and 1,310 in the fourth epoch (24 months of continuous treatment). The number (%) of patient treatment episodes in each treatment group in each of the four epochs is summarised in Table I. Approximately 50% of the patients in each epoch received olanzapine mono-therapy, reflecting the design of the study of enrolling approximately 50% of patients to olanzapine and 50% to non-olanzapine therapy.

Table II summarises the baseline socio-demographic and clinical characteristics of patients in the first treatment episode (0 to 6 months). There were major differences in the baseline socio-demographic characteristics between patients taking different treatments. Patients taking clozapine tended to be more frequently male, had a lower mean age, a higher clinical severity and less frequently lived independently. Patients taking depot typical antipsychotics were also more

Tab. I. Number (%) of patient treatment episodes in each treatment group by duration of treatment episode (epoch). *Numero (%) di pazienti in ciascun gruppo di trattamento per durata di trattamento (epoch).*

Epoch (months of continuous treatment)	Olanzapine	Risperidone	Quetiapine	Clozapine	Oral typical	Depot typical	Total
Epoch 1 (6)	1195 (43.8)	505 (18.5)	273 (10.0)	213 (7.8)	327 (12.0)	213 (7.8)	2726 (100)
Epoch 2 (12)	975 (47.4)	383 (18.6)	161 (7.8)	169 (8.2)	226 (11.0)	143 (7.0)	2057 (100)
Epoch 3 (18)	806 (49.5)	297 (18.2)	112 (6.9)	142 (8.7)	166 (10.2)	106 (6.5)	1629 (100)
Epoch 4 (24)	680 (51.9)	235 (17.9)	85 (6.5)	116 (8.9)	130 (9.9)	64 (4.9)	1310 (100)

Tab. II. Baseline patient characteristics of 0-6 month treatment episodes stratified by the medication prescribed during the episode. *Caratteristiche basali dei pazienti inclusi nel periodo di trattamento 0-6 mesi, per farmaco prescritto nel periodo considerato.*

	Olanzapine (n = 1195)	Risperidone (n = 505)	Quetiapine (n = 273)	Clozapine (n = 213)	Oral typical (n = 327)	Depot typical (n = 213)
Age, yrs	39.3 (12.8)	39.6 (13.0)	39.8 (12.7)	35.4 (10.5)	41.9 (12.9)	41.6 (11.7)
Sex, % male	58.0	56.5	51.7	67.5	47.9	65.3
Age at first contact, yrs	27.7 (9.9)	27.3 (9.4)	26.7 (9.4)	23.0 (6.2)	27.8 (9.2)	28.1 (9.6)
Paid employment, % yes	19.5	16.0	16.0	16.3	15.1	14.1
Social activities, % yes	64.7	66.3	69.4	63.2	65.6	65.6
Independent housing, %	35.1	35.6	34.4	25.2	34.6	45.8
Relationship, % yes	26.7	25.8	21.8	16.0	28.1	25.7
EPS, % yes	35.5	33.9	28.3	30.7	30.0	35.4
CGI-overall	4.3 (1.0)	4.2 (1.1)	4.1 (1.2)	4.5 (1.1)	4.1 (1.2)	4.0 (1.2)
EQ-VAS	45.9 (21.3)	49.1 (20.9)	50.5 (21.6)	44.8 (22.1)	47.9 (22.6)	54.9 (21.7)
Weight	73.0 (15.4)	75.2 (16.3)	75.9 (16.7)	77.5 (16.5)	74.4 (15.4)	77.5 (16.5)
BMI	25.8 (4.8)	26.8 (5.7)	27.0 (5.4)	26.3 (4.6)	26.7 (4.8)	27.4 (5.1)

Data presented as mean (SD) unless indicated otherwise.

Tab. III. Antipsychotic dosages used during the four epochs of continuous treatment (6, 12, 18 and 24 months). *Dosaggi medi e mediani giornalieri dei diversi antipsicotici utilizzati in monoterapia nelle quattro epoch considerate nello studio (6, 12, 18 e 24 mesi).*

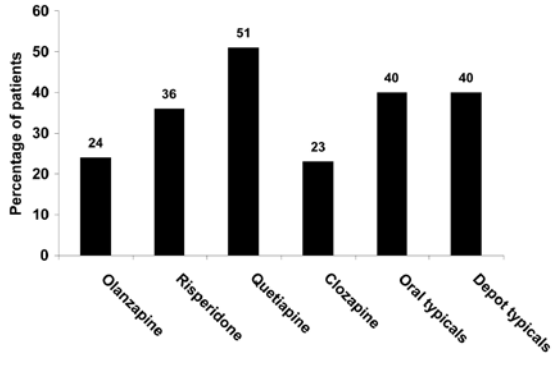
		Dose at 6 months	Dose at 12 months	Dose at 18 months	Dose at 24 months
Olanzapine	Mean (SD)	12.8 (5.9)	12.7 (6.2)	12.5 (6.0)	12.5 (6.3)
	Median	10	10	10	10
Risperidone	Mean (SD)	4.3 (2.2)	4.2 (2.2)	4.2 (2.2)	4.2 (2.2)
	Median	4	4	4	4
Quetiapine	Mean (SD)	389.9 (216.4)	407.8 (229.9)	402.6 (236.3)	403.9 (229.9)
	Median	400	400	400	400
Clozapine	Mean (SD)	244.8 (133.5)	254.3 (137.0)	247.1 (139.7)	247.5 (135.4)
	Median	250	250	250	300

frequently male and a higher proportion lived independently.

The median doses of olanzapine, risperidone and quetiapine were similar in all four epochs, whereas the median dose was higher in patients receiving clozapine for 24 months (300 mg/day) than in those receiving clozapine for 6, 12, or 18 months (250 mg/day) as shown in Table III. The doses of oral and depot typical antipsychotics are not shown as many different preparations were used and chlorpromazine equivalents have not been calculated.

The percentage of patients who changed the antipsychotic treatment initiated at baseline during the two years follow-up varied according to antipsychotic, ranging from 23% with clozapine to 51% with quetiapine (Fig. 1). The reasons for discontinuation of the antipsychotic given by the treating psychiatrist (more than one reason could be given) were: lack of efficacy (50%), lack of compliance (23%), patient request (21%) and intolerability (20%). A logistic regression model that compared the frequency of changing treatment of the different antipsychotics, adjusting by baseline covariates, showed that, compared with olanzapine, the odds ratios for likelihood of change of the initial antipsychotic over 24 months of treatment was significantly higher for risperidone (OR 1.78; 95% CI 1.39-2.30), quetiapine (OR 2.98; 95% CI 2.18-4.08), oral typicals (OR 2.01; 95% CI 1.43-2.82) and depot typicals (OR 2.01; 95% CI 1.26-3.21), but not significantly different for clozapine (OR 0.80; 95% CI 0.51-1.24). Patients were more likely to discontinue the antipsychotic drug they initiated at baseline if they were on antipsychotic treatment in the 6 months prior to entering the study (OR 1.89; 95% CI 1.34-2.68), had alcohol dependency at baseline (OR 2.39; 95% CI 1.21-4.71) and had a higher CGI-overall severity score (OR 1.20; 95% CI 1.08-1.32). Patients were less likely to discontinue their initial medication if they changed antipsychotic at baseline because of intolerability to prior treatment (OR 0.76; 95% CI 0.59-0.98).

Fig. 1. Proportion of patients who discontinued the antipsychotic they initiated at baseline by treatment group. *Percentuale di pazienti che hanno interrotto l'antipsicotico utilizzato al baseline, per gruppo di trattamento.*



Clinical effectiveness

CGI-overall was reduced from baseline after continuous treatment for 6, 12, 18 and 24 months in each of the treatment cohorts. The magnitude of the change in CGI-overall (Fig. 2) increased with increasing duration of treatment. Multivariate analysis showed that, compared with olanzapine, there was significantly less improvement in CGI-overall for risperidone, quetiapine, oral typical and depot typical antipsychotics in all four epochs, but no significant difference for clozapine (Tab. IV). For example, after adjusting for baseline differences, patients treated with risperidone improved by a mean 0.22 points of CGI-overall less than patients treated with olanzapine during the first 6 months of treatment. For the patients who were treated for at least 12 months, the cumulative difference in CGI-overall was 0.27.

Fig. 2. Change in CGI-overall from baseline for patients receiving continuous treatment for 6, 12, 18 and 24 months by treatment group. *Variazione nel CGI totale rispetto al basale in pazienti che ricevono terapia continuata per 6, 12, 18 e 24 mesi per gruppo di trattamento.*

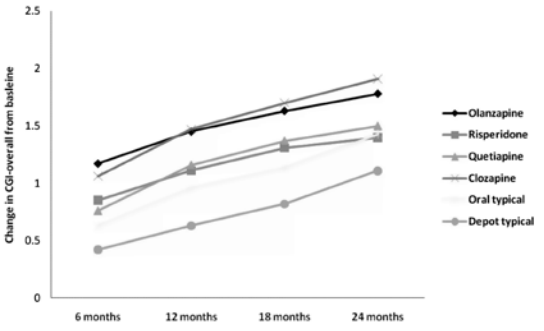
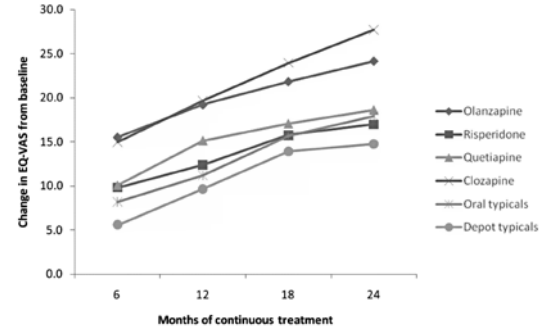


Fig. 3. Change in EQ-VAS from baseline for patients receiving continuous treatment for 6, 12, 18 and 24 months by treatment group. *Variazione nell'EQ-VAS rispetto al basale in pazienti che ricevono terapia continuata per 6, 12, 18 e 24 mesi per gruppo di trattamento.*



For each of the CGI positive, negative, depressive and cognitive symptoms, multivariate analysis showed there was significantly less improvement for typical antipsychotics (oral and depot) compared with olanzapine for 6, 12, 18 and 24 months of continuous treatment. In addition, compared with olanzapine, there was significantly less improvement in CGI positive symptoms with 6 and 24 months of continuous treatment with quetiapine; significantly less improvement in CGI negative symptoms with 6 to 24 months of risperidone, 6, 12 and 24 months of quetiapine, and 6 and 24 months of clozapine treatment; significantly less improvement in CGI depressive symptoms with 12 months of risperidone and 12 and 18 months of quetiapine treatment; and significantly less improvement in CGI cognitive symptoms with 6 to 24 months of risperidone and 6 and 12 months of quetiapine treatment.

Quality of life

Patient QoL improved during antipsychotic treatment; the EQ-VAS score increased from baseline in all treatment groups after 6, 12, 18 and 24 months of continuous treatment (Fig. 3). Multivariate analysis showed that patients receiving continuous risperidone for 6, 12 or 24 months or continuous oral typicals for 6, 12, 18 and 24 months had a significantly worse EQ-VAS score than patients receiving continuous olanzapine for the same duration (Tab. V).

Social functioning

There was an increase from baseline in the percentage of patients with social activities after 6, 12, 18 and 24 months of continuous treatment in all treatment groups (data not shown). Table V shows the results of the logistic model that compared the percentage of patients with social activities in each of the treat-

Tab. IV. Adjusted difference in CGI-overall score (95% CI) between olanzapine and other antipsychotic treatments after 6, 12, 18 and 24 months of continuous treatment (epoch analysis). *Differenze nel punteggio totale della scala CGI (IC 95%) tra olanzapina e gli altri trattamenti antipsicotici dopo 6, 12, 18 e 24 mesi di trattamento continuato (analisi epoch).*

Treatment duration	Olanzapine	Risperidone	Quetiapine	Clozapine	Oral typical	Depot typical
6 months	0	0.22 (0.11, 0.34)*	0.18 (0.03, 0.33)†	0.07 (-0.09, 0.23)	0.29 (0.15, 0.43)*	0.33 (0.16, 0.50)*
12 months	0	0.27 (0.14, 0.40)*	0.23 (0.05, 0.42)†	0.13 (-0.05, 0.31)	0.38 (0.21, 0.55)*	0.44 (0.24, 0.65)*
18 months	0	0.25 (0.10, 0.40)‡	0.25 (0.03, 0.47)†	0.13 (-0.06, 0.33)	0.31 (0.12, 0.51)‡	0.44 (0.20, 0.68)*
24 months	0	0.25 (0.08, 0.42)‡	0.30 (0.04, 0.56)†	0.17 (-0.04, 0.39)	0.29 (0.07, 0.51)‡	0.44 (0.15, 0.73)‡

A positive estimate indicates that olanzapine caused a greater improvement in symptom severity than the comparator antipsychotic.
* $p < 0.001$ *versus* olanzapine; † $p < 0.05$; ‡ $p < 0.01$.

Tab. V. Differences in quality of life and social functioning outcomes between olanzapine and the other treatment cohorts. Results from linear (EQ-VAS, results indicate adjusted mean difference and 95% CI) and logistic (social activities and paid employment, results indicate odds ratios and 95% CI) models. *Differenza nella qualità della vita e nella funzionalità sociale tra olanzapina e le alter coorti di trattamento. Risultati dei modelli lineare (EQ-VAS, I risultati indicano la differenza media aggiustata e 95% IC) e logistico (attività sociali e lavoro retribuito, i risultati indicano la odds ratio e 95% IC).*

	Olanzapine	Risperidone	Quetiapine	Clozapine	Oral typical	Depot typical
EQ-VAS						
6 months	0	-2.85 (-4.86, -0.84)*	-1.31 (-3.89, 1.26)	-0.36 (-3.14, 2.42)	-4.52 (-6.95, -2.08)†	-2.89 (-5.85, 0.07)
12 months	0	-3.14 (-5.47, -0.82)*	-1.08 (-4.35, 2.20)	0.50 (-2.63, 3.63)	-7.23 (-10.14, -4.32)†	-2.70 (-6.34, 0.94)
18 months	0	-2.49 (-5.06, 0.08)	-2.87 (-6.73, 1.00)	0.70 (-2.64, 4.04)	-6.10 (-9.40, -2.80)†	-0.05 (-4.09, 3.98)
24 months	0	-3.56 (-6.31, -0.81)‡	-3.27 (-7.49, 0.94)	-0.74 (-4.23, 2.76)	-8.36 (-11.86, -4.86)†	-3.32 (-7.91, 1.28)
Social activities						
6 months	1	0.86 (0.61, 1.22)	0.68 (0.43, 1.08)	0.62 (0.39, 0.99)‡	0.61 (0.39, 0.94)‡	0.46 (0.27, 0.79)*
12 months	1	1.09 (0.68, 1.74)	0.64 (0.35, 1.17)	0.45 (0.26, 0.77)*	0.51 (0.31, 0.86)‡	0.71 (0.38, 1.34)
18 months	1	0.85 (0.50, 1.46)	0.75 (0.35, 1.60)	0.36 (0.20, 0.67)*	0.65 (0.35, 1.23)	0.63 (0.30, 1.32)
24 months	1	0.97 (0.53, 1.80)	0.70 (0.30, 1.63)	0.70 (0.34, 1.42)	0.84 (0.41, 1.74)	0.97 (0.38, 2.52)
Paid employment						
6 months	1	1.05 (0.65, 1.69)	0.48 (0.23, 0.98)‡	0.44 (0.22, 0.85)‡	0.68 (0.34, 1.38)	0.69 (0.33, 1.46)
12 months	1	0.94 (0.55, 1.59)	0.77 (0.36, 1.63)	0.50 (0.24, 1.06)	0.52 (0.26, 1.06)	0.53 (0.21, 1.33)
18 months	1	0.77 (0.45, 1.32)	0.74 (0.32, 1.70)	0.42 (0.20, 0.88)‡	0.59 (0.28, 1.26)	0.35 (0.12, 0.98)‡
24 months	1	0.38 (0.20, 0.74)*	0.68 (0.26, 1.80)	0.47 (0.21, 1.07)	0.63 (0.28, 1.42)	0.46 (0.14, 1.46)

A negative estimate (for EQ-VAS) and an odds ratio < 1 (for social activities and paid employment) indicates treatment was worse than olanzapine.
* $p < 0.01$; † $p < 0.001$ *versus* olanzapine; ‡ $p < 0.05$.

ment cohorts. Patients treated with olanzapine had significantly more social activities compared with those treated with clozapine (6, 12 and 18 months of continuous treatment), oral typicals (6 and 12 months of continuous treatment) and depot typicals (6 months of continuous treatment).

There was a small increase in the percentage of patients with paid employment after continuous treatment for 6, 12, 18 and 24 months in the treatment groups (data not shown). Multivariate analysis showed a few differences between olanzapine and the other treatment groups that reached statistical significance (Tab. V). Compared with olanzapine, there were significantly fewer patients in paid employment after clozapine treatment for 6 or 18 months, risperidone for 24 months, depot typicals for 18 months and quetiapine for 6 months.

Tolerability

The proportion of patients with EPS decreased from the baseline value during antipsychotic treatment in all four epochs, regardless of the antipsychotic used (Tab. VI). Multivariate analysis showed that there were significantly fewer patients with EPS in the olanzapine group compared with the risperidone, oral typical and depot typical groups for all durations of continuous treatment from 6 months to 24 months (Tab. VI).

Figure 4 shows there was an increase in mean weight from baseline during 6, 12, 18 and 24 months of continuous treatment in all treatment groups. The increase in weight was greatest for the olanzapine and clozapine groups, but the pattern of weight gain was different with these two antipsychotics. Patients

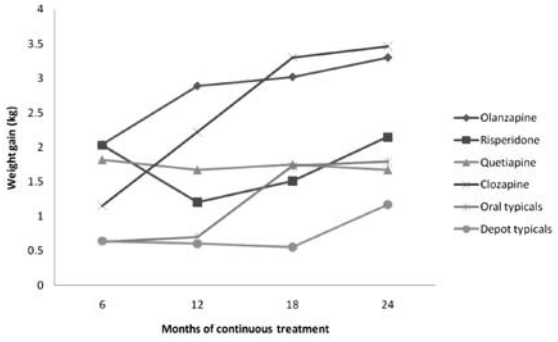
Tab. VI. Percentage of patient treatment episodes and odds ratio (95% CI) of having EPS during antipsychotic treatment versus olanzapine by duration of continuous treatment (epoch analysis). *Percentuale di pazienti con EPS e odds ratio (IC 95%) vs. olanzapina nel corso della terapia antipsicotica per durata del trattamento (analisi epoch).*

Duration of continuous treatment	Olanzapine	Risperidone	Quetiapine	Clozapine	Oral typical	Depot typical
6 months						
Baseline (%)	35.5	33.9	28.3	30.7	30.0	35.4
6 months (%)	8.5	18.6	9.3	11.3	26.7	32.9
OR (95% CI)	1	2.50 (1.70, 3.57)*	0.97 (0.56, 1.68)	1.37 (0.76, 2.47)	4.23 (2.83, 6.33)*	5.87 (3.57, 9.67)*
12 months						
Baseline (%)	37.3	32.1	30.0	33.1	32.6	37.1
12 months (%)	7.7	15.8	8.8	10.1	26.7	26.8
OR (95% CI)	1	2.86 (1.80, 4.54)*	1.50 (0.75, 3.02)	1.52 (0.79, 2.93)	6.02 (3.62, 10.04)*	5.37 (2.90, 9.95)*
18 months						
Baseline (%)	38.4	32.4	31.5	35.9	36.6	36.9
18 months (%)	7.1	13.9	8.0	8.8	22.0	24.5
OR (95% CI)	1	2.57 (1.47, 4.51)†	2.06 (0.89, 4.77)	1.42 (0.63, 3.22)	4.39 (2.34, 8.21)*	6.29 (3.05, 12.97)*
24 months						
Baseline (%)	39.3	34.5	29.4	38.8	41.1	41.3
24 months (%)	6.1	15.9	9.5	9.5	21.7	28.1
OR (95% CI)	1	3.73 (1.98, 7.03)*	2.64 (0.92, 7.58)	1.92 (0.79, 4.67)	5.76 (2.76, 12.02)*	10.15 (4.34, 23.76)*

Odds ratio (95% CI) adjusted by baseline values. An odds ratio > 1 indicates treatment was worse than olanzapine.
* $p < 0.001$ *vs.* olanzapine; † $p < 0.01$.

receiving olanzapine continuously for 6 months had a rapid increase in weight from baseline of mean 2.0 kg (2.8%) while in patients with more extended olanzapine treatment, the mean (%) increase in weight from baseline was 2.9 kg (4.0%), 3.0 kg (4.2%) and 3.3 kg (4.6%) for 12, 18 and 24 months, respectively. In contrast, there was a progressive increase in weight from baseline in patients receiving a longer duration of clozapine treatment; mean increase was1.2 kg (1.5%), 2.2 kg (2.9%), 3.3 kg (4.2%) and 3.5 kg (4.5%) among patients receiving continuous clozapine for 6, 12, 18 and 24 months, respectively.

Fig. 4. Change in weight (kg) from baseline for patients receiving continuous treatment for 6, 12, 18 and 24 months by treatment group. *Variazione di peso (kg) rispetto al basale in pazienti che ricevono terapia continuata per 6, 12, 18 e 24 mesi per gruppo di trattamento.*



Discussion

Using data from the Italian outpatients with schizophrenia taking part in the SOHO study, we have examined the effectiveness of treatment with various antipsychotics over a 24-month period. We found that a large proportion of the patients maintained the treatment started at baseline during the 2 years of follow-up. Patients starting treatment with olanzapine or clozapine were less likely to discontinue their medication than patients starting other types of antipsychotic at the baseline visit. The higher treatment maintenance with olanzapine is consistent with the results of Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) [28]. Although all the antipsychotic drugs used improved clinical symptoms, QoL and social functioning, there were significant differences between the various antipsychotic drugs for these outcomes and in their tolerability profiles. Notably, olanzapine

and clozapine were the most effective drugs and were similarly effective at improving clinical symptoms and QoL. Both olanzapine and clozapine were associated with a lower incidence of EPS but greater weight gain than the other antipsychotics, and the pattern of weight change over time differed between these two drugs.

This is one of the first studies to use epoch analysis for analysing outcome data from an observational study of the treatment of schizophrenia. This novel approach, when used to analyse the outcomes of medication treatment, allows the analysis of all information that each patient provides, also taking into account medication changes. Therefore, our results not only include those patients who respond to or tolerate their initial medication, but also patients who changed medication for various reasons, and probably more closely reflects the entire population of outpatients with schizophrenia.

These results are consistent with previous reports from the total SOHO study population and the 12-month results from the subgroup of Italian patients, and show that clozapine and olanzapine were the most effective antipsychotics [20 21]. In the present analysis, we found that clozapine and olanzapine were similarly effective on clinical symptoms (CGI) and QoL (EQ-VAS). In agreement with previous studies, we showed that typical antipsychotics were less effective than atypical antipsychotics; compared with continuous olanzapine treatment for 6, 12, 18 or 24 months, continuous treatment with oral typical antipsychotics was significantly less effective at improving clinical symptoms and QoL. Patients treated with clozapine appeared to have a lower percentage of adequate social functioning, as measured with the number of social activities and having paid employment. However, this may be due to the fact that patients being prescribed clozapine are treatment resistant and probably less prone to improvement in social functioning.

There was a reduction in the percentage of patients with EPS during treatment in all antipsychotic groups, but the greatest improvements were seen in the olanzapine, clozapine and quetiapine groups. Not surprisingly, typical antipsychotics (oral and depot) caused a higher incidence of EPS than olanzapine. Risperidone treatment was also associated with a significantly higher incidence of EPS than olanzapine, regardless of the duration of continuous treatment. These findings confirm earlier reports from the SOHO study [29] and a meta-analysis of RCTs [30], which concluded that olanzapine has a more favourable EPS profile than many other antipsychotics. Among the atypical antipsychotics, risperidone is known to have a higher EPS liability [31 32]. In a recent review, Weiden [32] pointed out that the likelihood of developing EPS was dependent not only upon the specific antipsychotic used, but also on the dosage and the individual patient's susceptibility to EPS. The significantly higher incidence of EPS in the oral typical and risperidone groups may have affected patient QoLand contributed to the significantly poorer improvement in EQ-VAS in those groups compared with the improvement seen in the olanzapine group.

An increase in weight is one of the major concerns regarding treatment with olanzapine or clozapine [33] and substantial weight gain may compromise long-term adherence with these medications [34]. Olanzapine and clozapine were associated with the greatest weight gain, but the pattern of weight gain was somewhat different. Olanzapine was associated with a mean increase in weight of 2.0 kg in the first 6 months of treatment, but the rate of weight gain then appeared to slow down and, over 24 months of continuous treatment, was less than that seen with clozapine, which was associated with a continuous increase in weight over time. Moreover, although olanzapine and clozapine were associated with the greatest weight gain, they were associated with the lowest incidence and likelihood of discontinuation of initial medication. It is possible that, for many patients, the greater improvements in symptoms, QoL and social functioning, and greater reduction in EPS outweigh the negative impact of weight gain.

Despite the strengths of the study, there are some limitations that must be mentioned. First, to be able to study the impact of each antipsychotic drug, we have restricted our analyses to those patients prescribed only one antipsychotic medication. By doing so, we may have excluded patients with more severe problems, thereby biasing the sample. Second, as the SOHO study was focused on olanzapine, the study design included over-sampling of the olanzapine group. Thus, the overall sample of patients is not directly representative of the population of patients starting a new antipsychotic in the outpatient setting. However, this does not directly affect the results of the epoch analysis where the focus of the analysis is the long-term effects of each medication studied and in which differences in sample size are taken into account. Moreover, the large sample of olanzapine-treated patients enabled precise outcome estimates to be obtained and allowed us to focus on the comparison of olanzapine versus each of the other antipsychotics. Third, the observational nature of the study meant that the psychiatrists were not blinded to treatment and this may have introduced selection and observer bias. However, selection bias was controlled by adjusting for baseline co-variates in the analyses and a specific analysis could not detect the presence of observer bias in the SOHO study [35].

In conclusion, the 24-month results of the SOHO study show that Italian outpatients with schizophrenia experience improvements in clinical symptoms, QoL

and social functioning during continuous treatment with various antipsychotics. Olanzapine and clozapine seem to be the most clinically effective antipsychotics. The tolerability profiles of the different antipsychotics vary, with olanzpaine and clozapine having less EPS, but more weight gain. Given the observational nature of the SOHO study, the results should be interpreted conservatively.

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