European Neuropsychopharmacology (2006) xx, xxx–xxx

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Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: Observational versus randomized studies results ☆

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Received 21 June 2006; received in revised form 9 September 2006; accepted 22 September 2006

KEYWORDS
Antipsychotics;
Effectiveness;
Clinical outcome;
Schizophrenia

Abstract Antipsychotic discontinuation rates are a powerful indicator of medication effectiveness in schizophrenia. We examined antipsychotic discontinuation in the Schizophrenia Outpatient Health Outcomes (SOHO) study, a 3-year prospective, observational study in outpatients with schizophrenia in 10 European countries. Patients (n=7728) who started antipsychotic monotherapy were analyzed. Medication discontinuation for any cause ranged from 34% and 36% for clozapine and olanzapine, respectively, to 66% for quetiapine. Compared to olanzapine, the risk of treatment discontinuation before 36 months was significantly higher for quetiapine, risperidone, amisulpride, and typical antipsychotics (oral and depot), but similar for clozapine. Longer medication maintenance was associated with being socially active and having a longer time since first treatment contact for schizophrenia, whereas higher symptom severity, treatment with mood stabilizers, substance abuse, having hostile behaviour were associated with lower medication maintenance. Antipsychotic maintenance in SOHO was higher than the results of previous randomized studies.

1. Introduction

The use of pragmatic measures in treatment trials facilitates the translation of study results into relevant clinical interpretations. In schizophrenia, given that antipsychotic treatment needs to be maintained for long periods of time, medication continuation or change is a powerful indicator of

☆ Sources of support: Josep Maria Haro and Dieter Naber have received economic compensation for their participation in the SOHO Advisory Board. David Suarez is Statistical Consultant for the SOHO study. Diego Novick and Jacqueline Brown are Lilly employees.
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doi:10.1016/j.euroneuro.2006.09.005

Please cite this article as: Haro, J.M. et al. Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: Observational versus randomized studies results. Eur. Neuropsychopharmacol. (2006), doi:10.1016/j.euroneuro.2006.09.005

medication usefulness. When a doctor or patient decides to change medication, it indicates that the treatment does not match the patient or doctor expectations, usually because of lack of effectiveness, tolerability problems or a combination of both (Swartz et al., 2003).

The recently conducted Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, a double-blind, randomized study that compared atypical and typical antipsychotics, used medication discontinuation as the main outcome measure of study medication effectiveness (Lieberman et al., 2005). The study reported high antipsychotic discontinuation rates at 18 months of follow-up, which ranged between 64% and 82% depending on medication. Compared to previous randomized studies, the CATIE study design included several improvements that increased the external validity of the results: possibility of concomitant medication use, dose changes during treatment, and broad inclusion criteria (Stroup et al., 2003). However, the antipsychotic discontinuation rates were surprisingly high, especially when compared to those reported in usual clinical practice (Covell et al., 2002). Some aspects of the CATIE study design could be causing this difference in discontinuation rates. In usual clinical practice, patients and doctors know the medication that is prescribed. Although the benefits of blinding in the control of observer bias in treatment studies are well known (Sacket et al., 1985), receiving an unknown medication may decrease confidence with that medication which, in turn, may increase the chances of medication change (Lieberman et al., 2005). Besides, a particular aspect of CATIE was that patients were switched to another antipsychotic when the patient or the doctor was not satisfied with either efficacy or tolerability. Given that discontinuation did not mean the end of the trial but end of first medication, beginning of another one, that was also free, patients and doctors may have been more prone to medication changes.

The Schizophrenia Outpatient Health Outcomes (SOHO) study, a 3-year observational, longitudinal study on the effectiveness of antipsychotic treatment for schizophrenia in the outpatient setting (Haro et al., 2003a), provides an excellent opportunity to analyze treatment discontinuation in routine clinical practice. The main objectives of this paper are to describe and compare the treatment discontinuation rates of typical and atypical antipsychotic medications in outpatients with schizophrenia taking part in the SOHO study. We will also explore other measures of treatment effectiveness such as medication tolerability.

2. Methods

The SOHO study was conducted in 10 European countries. One thousand and ninety-six investigators participated and enrolled at least one patient. Participating psychiatrists offered enrolment to patients with a clinical diagnosis of schizophrenia, aged 18 years or older, who were initiating or changing antipsychotic medication for the treatment of schizophrenia, who presented within the normal course of outpatient care and who were not participating in an interventional study. Patients were included irrespective of the reason for treatment change (e.g., lack of response, tolerability problems, etc.), and regardless of whether an antipsychotic drug

Table 1 Baseline sociodemographic and clinical characteristics by treatment cohort and for the total population

	Olanzapine (n=4247)	Risperidone (n=1549)	Quetiapine (n=583)	Amisulpride (n=256)	Clozapine (n=274)	Oral Typicals (n=471)	Depot Typicals (n=348)	Total (n=7728)
Age (years, mean ± SD)	39.7 ± 13.6	39.6 ± 13.4	40.5 ± 13.0	38.9 ± 12.9	36.5 ± 10.2	41.2 ± 12.9	42.1 ± 12.2	39.8 ± 13.3
Gender (% female)	42.2	42.3	48.4	45.9	37.7	52.0	43.8	43.3
Time since first treatment contact (years, mean ± SD)	10.2 ± 10.7	10.9 ± 11.3	11.9 ± 11.3	8.7 ± 9.2	12.0 ± 9.2	11.6 ± 10.7	12.3 ± 10.4	10.7 ± 10.8
First treatment ever (%)	14.3	13.6	4.1	10.2	1.8	9.2	6.0	12.1
Alcohol dependence (%)	2.6	3.3	3.1	3.9	2.6	2.6	5.2	2.9
Substance abuse (%)	2.7	2.7	1.9	3.9	1.5	1.5	4.9	2.7
Relationship with partner (%)	31.2	31.2	29.2	33.3	17.4	33.9	32.2	30.8
No social activities (%)	67.2	70.1	69.2	72.7	66.2	70.5	66.8	68.3
Working for pay (%)	21.9	21.6	15.4	24.8	14.7	20.0	15.9	20.8
Anticholinergics use (%)	9.4	21.6	8.8	10.2	8.8	27.2	30.8	13.9
Antidepressant use (%)	19.7	19.8	22.0	18.0	12.4	17.0	10.6	19.0
Anxiolytics use (%)	34.2	39.0	32.9	25.8	36.9	40.1	30.2	35.1
Mood stabilizers use (%)	9.2	8.6	11.2	5.9	18.6	9.6	7.2	9.4
Reason for discontinuation (%) [a]								
Lack of effectiveness	42.0	39.6	46.1	43.7	66.4	40.6	32.8	42.2
Intolerability	26.3	26.1	37.4	33.5	18.6	20.4	14.1	26.1
Lack of compliance	9.4	8.1	11.0	11.8	9.1	9.1	41.1	10.7
Patient request	18.7	19.8	29.4	33.1	16.4	24.8	19.5	20.6
CGI (mean ± SD)	4.39 ± 0.99	4.34 ± 0.97	4.33 ± 1.02	4.29 ± 0.95	4.77 ± 1.00	4.3 ± 1.09	4.39 ± 1.01	4.38 ± 1

CGI = clinical global impression; SD = standard deviation.
[a] More than one reason for discontinuation could be reported.

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Table 2 Outcome measures of treatment in the intention to treat medication

	Olanzapine ($n=4247$)	Risperidone ($n=1549$)	Quetiapine ($n=583$)	Amisulpride ($n=256$)	Clozapine ($n=274$)	Oral Typicals ($n=471$)	Depot Typicals ($n=348$)
Patients maintaining medication monotherapy at 36 months (n)	1851	619	126	85	123	141	121
Dose at baseline (mean ± SD, median)	10.6 ± 5.2, 10	4.4 ± 2.4, 4	249 ± 174, 200	362 ± 247, 400	149 ± 122, 100	–	–
Dose at last visit with baseline medication (mean ± SD, median)	11.8 ± 6.2, 10	4.8 ± 2.8, 4	377 ± 222, 400	407 ± 271, 400	239 ± 149, 200	–	–
Discontinuation for any cause							
Patients changing medication before 36 months (%)[a]	36.4	42.7	66.1	50.4	33.8	53.1	50.2
Kaplan-Meier time to discontinuation, 25% percentile (months)	15	9	4.5	4.5	15	5	9
Hazard ratio (95% CI)[b]	1	1.28 (1.16, 1.42)***	2.22 (2.00, 2.51)***	1.63 (1.33, 2.00)***	0.82 (0.66, 1.02)	1.70 (1.46, 1.97)***	1.43 (1.19, 1.70)***
Discontinuation for lack of efficacy							
Patients changing medication before 36 months (%)[a]	18.4	22.7	48.3	28.7	17.8	33.8	31.4
Hazard ratio (95% CI)[b]	1	1.32 (1.14, 1.53)***	2.85 (2.41, 3.36)***	1.92 (1.44, 2.56)***	0.74 (0.54, 1.02)	2.08 (1.71, 2.53)***	1.83 (1.45, 2.31)***
Discontinuation for intolerability							
Patients changing medication before 36 months (%)[a]	6.4	10.1	14.2	13.7	7.2	13.3	9.2
Hazard ratio (95% CI)[b]	1	1.67 (1.32, 2.10)***	2.33 (1.73, 3.15)***	2.55 (1.66, 3.91)***	1.16 (0.69, 1.94)	2.15 (1.54, 3.01)***	1.47 (0.95, 2.29)
Discontinuation for lack of compliance							
Patients changing medication before 36 months (%)[a]	9.0	12.4	17.8	15.6	8.9	12.8	9.9
Hazard ratio (95% CI)[b]	1	1.31 (1.06, 1.63)*	2.08 (1.56, 2.78)***	1.59 (1.03, 2.45)*	0.92 (0.58, 1.46)	1.58 (1.14, 2.20)**	0.89 (0.57, 1.38)
Discontinuation for patient request							
Patients changing medication before 36 months (%)[a]	11.4	12.3	17.6	13.2	6.2	17.0	15.3
Hazard ratio (95% CI)[b]	1	1.12 (0.91, 1.37)	1.55 (1.17, 2.06)**	1.14 (0.75, 1.75)	0.59 (0.34, 1.01)	1.49 (1.11, 2.01)**	1.37 (0.97, 1.94)
Duration of successful treatment							
Kaplan-Meier time of successful treatment, 25 percentile (months)	7.5	3	0.03	0.03	10.5	1.5	0.03
Hazard ratio (95% CI)[b]	1	1.28 (1.16, 1.41)***	2.26 (2.00, 2.55)***	1.70 (1.40, 2.07)***	0.89 (0.71, 1.11)	1.69 (1.46, 1.96)***	1.51 (1.27, 1.81)***

[a] Kaplan-Meier estimate.
[b] Cox model treatment comparison.
* $p<0.05$.
** $p<0.01$.
*** $p<0.001$.

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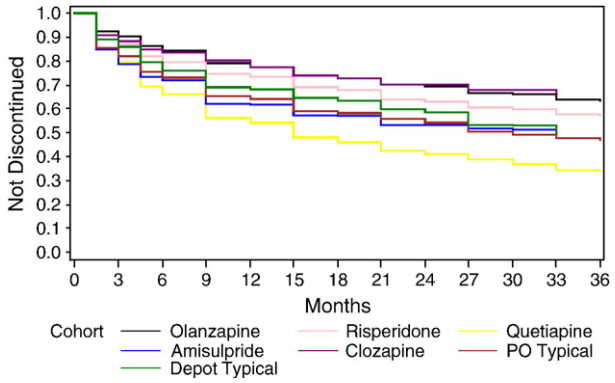

Figure 1 Kaplan-Meier of time to discontinuation for any cause by cohort.

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.

Since the initial objective of the SOHO study was to compare olanzapine with other antipsychotics, the study was designed to include two patient cohorts of approximately equal size; one starting olanzapine therapy and the other starting treatment with other antipsychotics. In most countries, to achieve this proportion, enrolment was conducted in a systematic alternating order; the first patient was recruited into the olanzapine cohort, the second patient into the non-olanzapine cohort, etc. Investigators were instructed to make treatment decisions independent of the study and then evaluate whether patients were eligible for inclusion based on the entry criteria and the alternating structure of enrolment. The recruitment period was intentionally long and no minimum number of cases was required by each investigator. Investigators in Spain and Ireland were asked to enroll a similar number of patients into each cohort, but were not required to enroll according to the alternating sequence. A total of 10 972 patients with schizophrenia were enrolled in the study.

All patient care was at the discretion of the participating psychiatrist. No instructions about patient care were included in the study description. Further details on the SOHO study design have been provided elsewhere (Haro et al., 2003a).

The study was approved in all countries either at the site, regional, or national level, depending on the country and local regulations. Patient consent followed country regulations. All patients gave at least oral informed consent and written informed consent was obtained in Denmark, Italy, Portugal, Spain, Ireland, and the UK.

Data collection for the study occurred during visits within the normal course of therapy and was targeted for baseline, 3, 6, 12, 18, 24, 30 and 36 months, with assessment allowed within 1 month either side of each target time point. Patients were visited when the psychiatrist decided following the normal course of care. These visits could be more frequent than the assessment points. Patients who were not seen during the normal course of care within one assessment interval were not excluded from subsequent data collection.

Clinical severity was assessed using a scale based on the Clinical Global Impression (CGI) (Guy, 1976), which evaluated positive, negative, cognitive, depressive and overall symptoms on the day of assessment. This was subsequently expanded and validated as the Clinical Global Impression-Schizophrenia scale (CGI-SCH) (Haro et al., 2003b), which evaluates symptom severity during the week preceding the day of assessment. The CGI and CGI-SCH are physician-rated scales with values ranging from 1 (not ill) to 7 (among the most severely ill patients).

Data collection included detailed information on the prescribed antipsychotic medication (name of antipsychotic, dose, and route of administration) and whether or not each of the following was used: anticholinergics, antidepressants, anxiolytics/hypnotics and mood stabilizers. At each visit, both the medication the patient was taking upon presentation and the medication prescribed at that visit were recorded. Reasons for medication change were also recorded and classified as lack of efficacy, intolerability, lack of compliance or patient request. More than one reason could be recorded for each medication change.

2.1. Statistical analysis

The patients included in the analysis are those who initiated treatment at baseline with only one antipsychotic (monotherapy). Patients who were on an antipsychotic medication before baseline, started a new antipsychotic at baseline and tapered down the previous medication before the 3-month visit were considered to be on antipsychotic monotherapy. Patients were classified into seven treatment cohorts according to the antipsychotic medication started at baseline: olanzapine, risperidone, amisulpride, quetiapine, clozapine, oral typicals and depot typicals.

Of the 9857 patients who started one of the above medications at baseline, 8072 (81.9%) initiated treatment as monotherapy. Of the monotherapy patients, 7728 (95.7%) had at least one follow-up visit and constitute the population that has been analyzed. Of these 7728 patients, 5205 (67.4%) had valid data for all time points. There were no cohort differences in the proportion of patients with information at all visits or of patients with missing information. For the survival analysis, the last observation for each patient was the one before the first missing visit.

Patients came from the ten countries participating in SOHO: Denmark (17 patients), France (714), Germany (2233), Greece (533), Ireland (30), Italy (2104), Netherlands (139), Portugal (78), Spain (1688), and UK (192 patients).

Treatment discontinuation was defined as stopping the antipsychotic medication started at baseline and/or adding of a new antipsychotic.

Kaplan-Meier survival curves were used to estimate the time to treatment discontinuation. For medication changes that occurred at assessment visits (e.g., 3, 6, or 12 months), the time of medication discontinuation used in the survival analysis was the month of the visit (e.g., 3, 6 or 12 months). For medication changes that occurred between assessment visits, the time of medication change was the mean time between the visits (e.g., 4.5 months for a medication change that occurred between the 3- and 6-month visits).

Cox regression models were used to compare the time to medication discontinuation between treatment groups. Since differences among the medication groups could exist at baseline, the

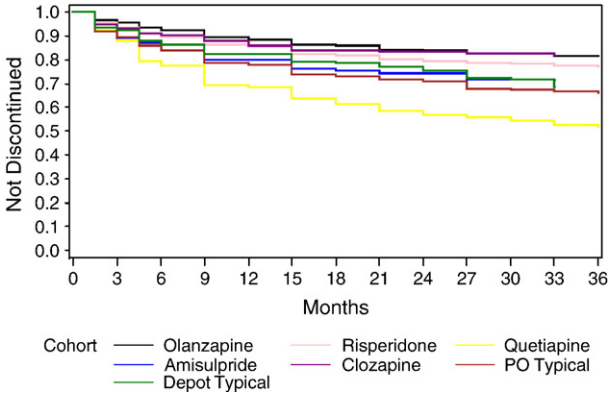

Figure 2 Kaplan-Meier of time to discontinuation for lack of efficacy by cohort.

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models included the characteristics of the patients at the baseline assessment to avoid that those variations were affecting treatment group differences. Only those variables that remained after performing a stepwise model reduction were kept. Different models were fitted for the overall analysis and the analysis stratified by reason for medication discontinuation. Data are presented as hazard ratios (HR) and 95% confidence intervals (CI).

Categorical data (numbers and percentages) for side effects present at baseline and at any time during follow-up until medication discontinuation are presented for each treatment cohort.

Treatment group comparisons in the changes in CGI scale scores from baseline over time were made using a mixed model (SAS version 9.0) including the same fixed covariates as for the time to discontinuation, plus baseline CGI score, time, the interaction between treatment and time, and the interaction between baseline CGI score and time. Time was classified into months (3, 6, 12, 18, 24, 30, and 36). The correlation of the repeated measures within each patient was modeled with the use of a random intercept and an unstructured covariance matrix.

Successful treatment time was defined as the total number of months of treatment before antipsychotic discontinuation in which patients had a CGI scale score of at most 3 (mildly ill) or a score of 4 (moderately ill) with an improvement of at least two points from baseline. Cox regression models were used to compare treatment cohorts in successful treatment time.

3. Results

The baseline sociodemographic and clinical characteristics of the 7728 patients included in the analysis are summarized in Table 1. Due to the study design, approximately half of the patients started olanzapine (n=4247, 55%) at the baseline visit. Of the total population, 43.3% were female and the mean (±standard deviation, SD) age was 39.8 (±13.3) years. Although 12.1% of the patients were receiving antipsychotic medication for the first time ever, most of the patients had a chronic course and the mean (±SD) time since first treatment contact for schizophrenia was 10.7 (±10.8) years. There were few major differences in the baseline characteristics among the treatment cohorts. Patients in the clozapine cohort tended to have a higher baseline CGI severity score and worse social functioning (lower frequency of relationship with partner and working for pay). A greater proportion of patients in the risperidone, oral typicals and depot typicals cohorts were using anticholinergics at the baseline visit compared to the other medication groups.

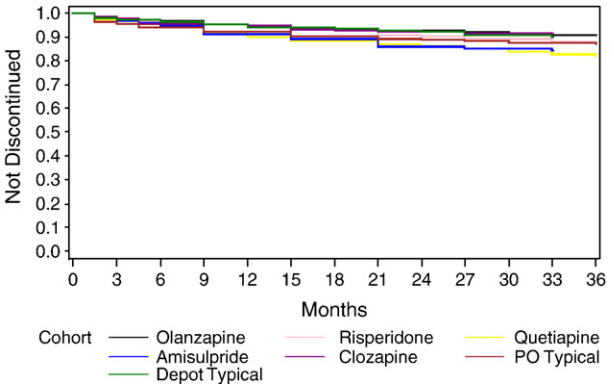

Figure 4 Kaplan-Meier of time to discontinuation for lack of compliance by cohort.

Patients taking typical antipsychotics were grouped due to the large number of medications used. In the 471 patients taking oral typicals, the medications used were: bromperidol (10 cases), chlorpromazine (18), clothiapine (10), flupenthixol (42), haloperidol (192), perazine (34), perphenazine (16), pimozide (24), sulpiride (21), thioridazine (21), trifluoperazine (21), zuclopenthixol (22). In the patients taking depot antipsychotics, the antipsychotics used were Flupenthixol (85 cases), Fluphenazine (75), Haloperidol (93), Zuclopenthixol (72).

Mean medication doses showed only small increases from baseline to 36 months or medication discontinuation in the olanzapine, risperidone and amisulpride cohorts (Table 2), but greater increases in the quetiapine and clozapine groups.

There were marked differences between treatment cohorts in the percentage of patients that discontinued medication for any reason: while 64% of the patients that started olanzapine at baseline maintained that medication at 36 months, only 34% of the patients starting quetiapine continued to take it at 36 months (Fig. 1). The Cox proportional hazard ratios (HR) of treatment discontinuation for any cause were higher for quetiapine, oral typicals, amisulpride, depot typicals and risperidone compared to olanzapine, whereas the hazard ratio for clozapine was similar to that of olanzapine (Table 2). These results are consistent with the conclusions of the Kaplan-Meier and are adjusted for baseline differences among the cohorts.

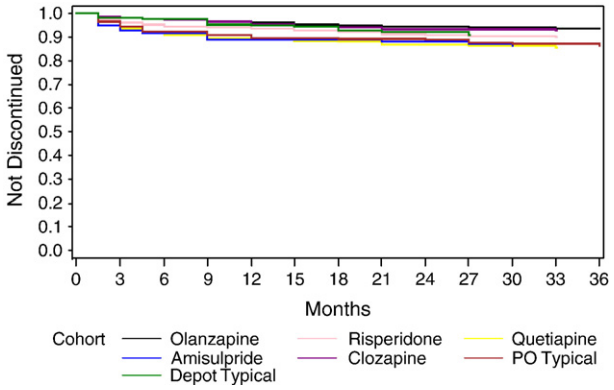

Figure 3 Kaplan-Meier of time to discontinuation for intolerability by cohort.

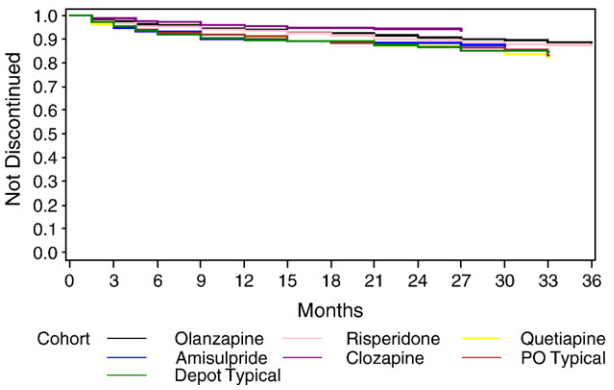

Figure 5 Kaplan-Meier of time to discontinuation because of patient request by cohort.

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Table 3 Outcome measures of tolerability and safety by treatment cohort

	Olanzapine	Risperidone	Quetiapine	Amisulpride	Clozapine	Oral Typicals	Depot Typicals
Hospitalization for exacerbation of schizophrenia							
Hospitalizations before medication discontinuation (*n*)	1103	375	171	92	92	152	153
Risk ratio of hospitalization before medication discontinuation (hospitalizations/ persons years)	0.14	0.14	0.23	0.25	0.17	0.21	0.26
Hazard ratio (95% CI) [a]	1	1.04 (0.88, 1.23)	1.64 (1.31, 2.05) ***	1.39 (1.01, 1.92) *	1.13 (0.83, 1.53)	1.39 (1.08, 1.79) **	1.44 (1.10, 1.88) **
Suicide attempt							
Six months before baseline (*n*)	200	60	22	17	15	19	17
Six months before baseline (%)	4.7	3.9	3.8	6.6	5.5	4.0	4.9
Present at any time during follow-up until medication discontinuation (*n*)	88	29	8	8	5	2	12
Present at any time during follow-up until medication discontinuation (%)	2.1	1.9	1.4	3.1	1.8	0.4	3.5
Extrapyramidal symptoms							
Baseline visit (*n*)	1551	541	204	89	105	142	129
Baseline visit (%)	36.5	34.9	35.0	34.8	38.3	30.2	37.1
Present at any time during follow-up until medication discontinuation (*n*)	622	499	78	43	47	148	149
Present at any time during follow-up until medication discontinuation (%)	14.7	32.2	13.4	16.8	17.2	31.4	42.8
Tardive dyskinesia							
Baseline visit (*n*)	368	124	61	31	29	39	31
Baseline visit (%)	8.7	8.0	10.5	12.1	10.6	8.3	8.9
Present at any time during follow-up until medication discontinuation (*n*)	249	121	35	25	17	41	45
Present at any time during follow-up until medication discontinuation (%)	5.9	7.8	6.0	9.8	6.2	8.7	12.9
Loss of libido/impotence							
Baseline visit (*n*)	2008	740	295	130	140	234	155
Baseline visit (%)	47.3	47.8	50.6	50.8	51.1	49.7	44.5
Present at any time during follow-up until medication discontinuation (*n*)	1990	808	232	126	133	239	173
Present at any time during follow-up until medication discontinuation (%)	46.9	52.2	39.8	49.2	48.5	50.7	49.7
Gynecomastia, galactorrhea, amenorrhea							
Baseline visit (*n*)	508	211	120	38	46	65	43
Baseline visit (%)	12.0	13.6	20.6	14.8	16.8	13.8	12.4

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Table 3 (*continued*)

	Olanzapine	Risperidone	Quetiapine	Amisulpride	Clozapine	Oral Typicals	Depot Typicals
Gynecomastia, galactorrhea, amenorrhea							
Present at any time during follow-up until medication discontinuation (*n*)	489	259	72	46	45	70	48
Present at any time during follow-up until medication discontinuation (%)	11.5	16.7	12.4	18.0	16.4	14.9	13.8
Weight change from baseline to 36 months or medication discontinuation							
Weight gain >7% (*n*)	1280	341	68	40	66	74	76
Weight gain >7% (%)	30.1	22.0	11.7	15.6	24.1	15.7	21.8
Mean (SD) weight change (kg)	3.6 (8.9)	2.5 (8.8)	0.6 (7.9)	0.5 (10.8)	3.0 (11.5)	1.5 (6.3)	2.6 (10.3)

[a] Cox model treatment comparison.
[*] $p<0.05$.
[**] $p<0.01$.
[***] $p<0.001$.

The analysis of medication discontinuation due to lack of efficacy was largely consistent with the analysis of discontinuation for any cause (Fig. 2 and Table 2). The Kaplan-Meier estimates of the percentage of patients discontinuing medication before 36 months due to intolerability (Fig. 3, Table 2), lack of compliance (Fig. 4, Table 2) or patient request (Fig. 5, Table 2) were lower than those for lack of efficacy, but the hazard ratios of treatment comparisons followed a similar pattern to those described for discontinuation due to any cause (Table 2).

The Cox regression model also allowed us to analyze factors associated with the rate of medication discontinuation due to any reason. Patients who received treatment for schizophrenia for the first time in their lives had a lower rate of medication discontinuation (HR 0.81; 95% CI 0.69, 0.94) compared with patients that had been on treatment before baseline. Also, being socially active (HR 0.87; 95% CI 0.80, 0.95) and having a longer time since first treatment contact for schizophrenia (HR 0.995 for each additional year; 95% CI 0.991, 0.999) were associated with longer treatment maintenance. Conversely, higher CGI severity at baseline (HR 1.11 for each additional point; 95% CI 1.05, 1.14), concomitant treatment with mood stabilizers (HR 1.18; 95% CI 1.04, 1.33), substance abuse (HR 1.26; 95% CI 1.01, 1.57), having had hostile behaviours in the 6 months prior to the baseline assessment (HR 1.11; 95% CI 1.02, 1.21), and effectiveness as reason for change at the baseline visit (HR 1.15; 95% CI 1.06, 1.24) were associated with lower medication maintenance.

Analysis of the duration of successful treatment showed significant differences in duration between patients who started olanzapine at baseline and those who started risperidone, quetiapine or typical antipsychotics at baseline (Table 2).

Table 3 shows the outcome measures of medication tolerability by treatment cohort. The hospitalization rate before medication discontinuation was lower for the patients who started olanzapine and risperidone compared with other medications (Fig. 6). No relevant differences were found in the proportions of suicide attempts by treatment cohort. Patients taking risperidone and typical antipsychotics showed a higher frequency of extrapyramidal symptoms (EPS) before medication discontinuation than patients taking other medications. Similarly, patients taking risperidone, amisulpride and typical antipsychotics had a higher frequency of tardive dyskinesia (TD) before medication discontinuation. Loss of libido and impotence was frequent among patients in all treatment cohorts at baseline and was present at any time during follow-up until medication change in 39.8% of patients in the quetiapine cohort to 50.7% and 52.3% patients in the oral typicals cohort and risperidone cohorts (Table 3). The results about side effects are descriptive and no statistical analysis has been conducted.

Weight gain was higher among patients receiving olanzapine than other antipsychotics, with a mean weight change of 3.6 kg from baseline until 36 months or medication discontinuation in the olanzapine cohort compared to figures ranging from 0.5 kg to 3.0 kg for the other medications (Table 3).

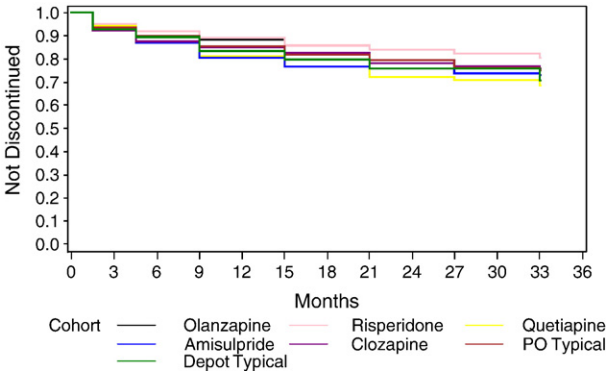

Figure 6 Kaplan-Meier of time to hospitalization.

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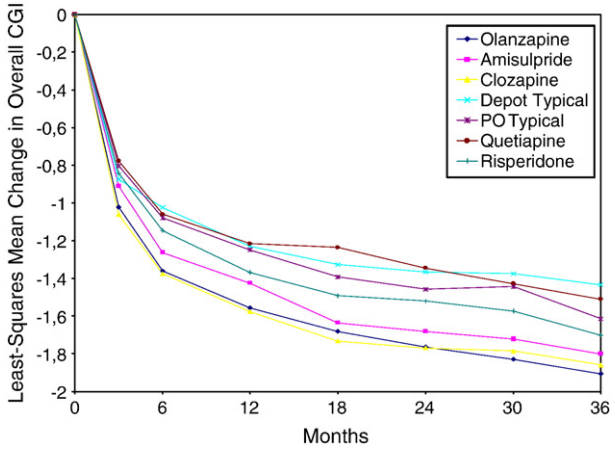

Figure 7 Least-squares mean change in CGI severity score.

Fig. 7 shows the least-squares mean change in CGI severity score during the 3 years follow-up. The results are largely consistent with the survival analysis models, since patients that has initiated treatment with olanzapine and clozapine showed the highest reduction in symptoms and patients treated with typical antipsychotics and quetiapine the lowest.

4. Discussion

Rates of antipsychotic treatment maintenance found in this 3-year prospective observational study were much higher than the findings of the CATIE study (Lieberman et al., 2005). While 64% to 82% of patients in the CATIE study discontinued their medication before 18 months of treatment, in the SOHO study, the figures for 18 months were between 28% and 55%, depending on the medication prescribed at baseline. Both studies were highly consistent in the finding that olanzapine showed the highest rates of medication maintenance, although we also found differences among other antipsychotics. Clozapine in our study showed similar discontinuation rates than olanzapine, and quetiapine was associated with the lowest medication maintenance. Patients starting clozapine were more severe that patients taking other antipsychotics, which is consistent with clozapine being used for treatment-resistant schizophrenia. This could also lead the treating psychiatrist to adhere longer to clozapine in contrast to other antipsychotics.

Antipsychotic treatment maintenance has been considered a good proxy measure of treatment effectiveness since it summarizes efficacy on disorder symptoms, tolerability and compliance (Swartz et al., 2003). The low rates of treatment maintenance in the CATIE study were interpreted as antipsychotic drugs having substantial limitations in their effectiveness (Lieberman et al., 2005). While antipsychotic medications do have important limitations, the medication maintenance rates found in our study and in studies based on the analysis of large databases (Covell et al., 2002; Williams et al., 1999) were much higher. The treatment discontinuation findings in the CATIE study are much nearer to those found in clinical trials (Wahlbeck et al., 2001) than in routine clinical practice. As mentioned before, the CATIE study design may the difference with our study findings. Also patients included in CATIE were less severe and improved less, as measured by the CGI, than patients included in SOHO.

Besides the finding that olanzapine and clozapine seemed to be the most effective antipsychotics analyzed, we also have observed that risperidone and typical antipsychotics were associated with more EPS, and that olanzapine was associated with greater weight gain. These results confirm and extend the 6- and 12-month results from the SOHO study, published previously (Haro et al., 2005, 2006a; Lambert et al., 2005). Our finding that olanzapine compared favourably with typical and some atypical antipsychotics supports the findings of the CATIE study, where the comparator antipsychotics were risperidone, quetiapine and ziprasidone; in the SOHO study, the comparator agents were risperidone, quetiapine and amisulpride (ziprasidone was not available in Europe at the time of study initiation). A recent study based on register data also found greater maintenance rates for olanzapine when compared to risperidone (Cooper et al., 2005). The SCAP study found olanzapine, clozapine and risperidone were associated to longer medication continuation (Ascher-Svanum et al., 2006a,b). The SOHO study findings of longer treatment maintenance with olanzapine were accompanied by a longer duration of successful treatment, lower rates of hospitalization and greater reduction in psychopathology.

Antipsychotic doses of atypicals used in the SOHO study were within the recommended ranges and similar to the doses employed in clinical trials for olanzapine, clozapine and risperidone (Tollefson et al., 1997; McGorry et al., 2003; Conley and Mahmoud, 2001). However, the doses of quetiapine and amisulpride for many patients were below the recommended doses, which are above 400 mg per day for both drugs (Curran and Perry, 2002; Cutler et al., 2002). Both drugs had only recently become available in Europe and participating psychiatrists could be less familiar with their use, which could have impacted negatively on the outcomes of these medications in SOHO.

Clinical factors associated to lower medication discontinuation were being socially active, and having a course of illness and not abusing substance nor having hostile behaviours, which is consistent with most previous findings (Janssen et al., 2006; Weiss et al., 2002; Ascher-Svanum et al., 2006a,b). Surprisingly, patients who received treatment for schizophrenia for the first time in their lives had a lower rate of medication discontinuation, which seems not agree with previous findings that age is related to better adherence (Valenstein et al., 2004). This could be caused by chronic patients included in SOHO being more severe since were included in SOHO since they needed a medication change.

Medication tolerability findings (higher rates of EPS and prolactin-related symptoms among patients taking risperidone and typical antipsychotics, lower rates of sexual-related side effects in patients taking quetiapine, and greater weight gain in olanzapine) were consistent with previous studies and reviews (Whitworth and Fleischhacker, 1995; Peuskens et al., 1998; Nasrallah, 2003; Leucht et al., 1999; Tarsy et al., 2002). Weight gain was greatest in the olanzapine cohort in the SOHO study, but was lower than the weight gain reported in the CATIE study. The tolerability findings in the SOHO study are limited in scope given that no laboratory tests were performed as part of the data collection process due to the observational nature of the study. Also, the results that

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have been reported about side effects are purely descriptive. Comparisons with the CATIE study should also take into account that the CATIE study did not include first episode patients or treatment-resistant patients.

Several limitations should be considered when discussing the results. First, only patients taking antipsychotic monotherapy were analyzed, which may imply that patients with the most severe disease were not included in the analyses. However, the frequency of combination therapy in the SOHO study was similar to that reported in other observational studies (Covell et al., 2002). Second, the SOHO study was an observational study and patients were not randomized to treatment. Although this is also one of the strengths of the study since it better reflects clinical practice, there could be unobserved differences between the medication cohorts that could not be adjusted for in the multivariate analysis and which, therefore, confound the study results. Methodological research has found that when properly conducted and analyzed, observational studies are valid in analyzing medication outcomes (Haro et al., 2006b). Third, unlike in the CATIE study, we cannot identify any individual side effect as the cause of treatment discontinuation, since participating psychiatrists could ascribe more than one reason for the medication discontinuation. Fourth, although retention rate was high, not all the patients were evaluated at follow-up and it is possible could be that attrition could be influencing the results. Fifth, the study included a large number of centres and investigators with different medical background and experience. Finally, because the study was powered to focus on olanzapine, we have only been able to compare olanzapine with other antipsychotics.

In conclusion, the findings from the SOHO study support the differences in antipsychotic effectiveness found in the CATIE study, but also show that antipsychotic effectiveness that it is obtained from randomized, double-blind clinical trials may be an underestimation of medication effectiveness in real life due to the design restriction of these types of studies. Randomized, but not blinded, studies may be a better approach to evaluating effectiveness.

Acknowledgements

The SOHO Study Group: (Denmark) Karsten Haderup Kristensen, Aalborg Psykiatrisk Hospital, Aalborg, Denmark; (France) Jean-Pierre Lepine, Hôpital Fernand Widal, Paris, France; (France) Isabelle Gasquet, Hôpital Paul Brousse, Villejuif, France; (Germany) Dieter Naber, Universitatskrankenhaus-Eppendorf, Klinik fur Psychiatrie und Psychotherapie, Hamburg, Germany; (Greece) Venetsanos G. Mavreas, Department of Psychiatry, University of Ioannina, Greece; (Ireland) Declan Murray, St. Ita's Hospital, Dublin, Ireland; (Italy) Paolo Pancheri, Fondazione Italiana per lo studio della Schizofrenia (FIS), Rome, Italy; (The Netherlands) CJ Slooff, Psychosencluster GGX N-Drenthe, Kenniscentrum Scizofrenie, RA Assen, The Netherlands; (Portugal) João Marques Teixeira, University do Porto, Porto, Portugal; (Spain) Jordi Alonso, Health Services Research Unit, Institut Municipal d'Investigacio Medica, University of Barcelona, Barcelona, Spain; (Spain) Josep Maria Haro, Research and Development Unit, Sant Joan de Déu-SSM, Sant Boi, Barcelona, Spain; (Spain) Manuel Bousoño, Universidad de Oviedo, Asturias, Spain; (UK) Tim Croudace, Department of Psychiatry, Addenbrooke's Hospital, Cambridge, UK; (UK) Peter B. Jones, University of Cambridge, Addenbrooke's Hospital, Cambridge, UK; (UK) Martin Knapp, London School of Economics, Centre for the Economics of Mental Health, Institute of Psychiatry, London, UK. David Suarez has received a research award from the Instituto de Salud Carlos III (Ministerio de Sanidad y Consumo, Spain FIS CA05/0177).

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Please cite this article as: Haro, J.M. et al. Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: Observational versus randomized studies results. Eur. Neuropsychopharmacol. (2006), doi:10.1016/j.euroneuro.2006.09.005

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Please cite this article as: Haro, J.M. et al. Three-year antipsychotic effectiveness in the outpatient care of schizophrenia: Observational versus randomized studies results. Eur. Neuropsychopharmacol. (2006), doi:10.1016/j.euroneuro.2006.09.005