Original article

The Schizophrenia Outpatient Health Outcomes (SOHO) study: 3-year results of antipsychotic treatment discontinuation and related clinical factors in Spain

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Abstract

Introduction. — This article presents the long-term results in terms of antipsychotic medication maintenance and factors influencing it in a representative sample of patients with schizophrenia recruited in the SOHO study within Spain.

Methods. — The SOHO was a prospective, 3-year observational study of the outcomes of schizophrenia treatment in outpatients who initiated therapy or changed to a new antipsychotic performed in 10 European countries with a focus on olanzapine. The Kaplan–Meier method was used to analyse the time to treatment discontinuation and the Cox proportional hazards model to investigate correlates of discontinuation.

Results and conclusions. — In total, 1688 patients were included in the analyses. Medication maintenance at 3 years varied with the antipsychotic prescribed, being highest with clozapine (57.6%, 95% CI 39.2–74.5), followed by olanzapine (48.3%, 95% CI 45.1–51.5); and lowest with quetiapine (19.0%, 95% CI 13.0–26.3). Treatment discontinuation was significantly less frequent with olanzapine than with risperidone (p = 0.015), depot typical (p = 0.001), oral typical antipsychotics (p < 0.001) or quetiapine (p < 0.001); but not than with clozapine (p = 0.309). Longer maintenance was also associated with higher social abilities and better cognitive status at baseline; in contrast, a shorter time to discontinuation was associated with the need for mood stabilisers during follow-up. This study emphasises the different value of antipsychotics in day-to-day clinical practice, as some of them were associated with longer medication maintenance periods than others. This study has some limitations because of possible selection and information biases derived from the non-systematic, non-randomised allocation to treatments and the existence of unobserved covariates that may influence the outcome.

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1. Introduction

The evidence coming from recent well-designed robust epidemiologic studies has reinforced the ancient notion of an adequate adherence to antipsychotic medication as a major contributor to prevent relapse and re-hospitalisation of patients with schizophrenia [23,24]. Further, current reports point unequivocally to continuous drug treatment as a determinant factor of therapeutic outcome in these patients [1,20].

In addition to effectiveness and tolerability, there are specific determinants that are known to affect maintenance of antipsychotic agents, like patient’s insight and the doctor—patient relationship [11,26]. Thus, long-term medication maintenance appears as a good indicator of the actual usefulness of antipsychotics in day-to-day clinical practice.
Whilst the efficacy and safety of second-generation antipsychotics in schizophrenia has been established by a series of key experimental clinical trials [19], in their routine practice clinicians may find it difficult to fully satisfy their need for an appropriate scientific basis to support therapeutic decisions based solely on the results of such experimental studies [14]. As these studies are (correctly) focused on relatively short-term measures of clinical severity, they can hardly provide reliable data on long-term medication durability [22].

Time to antipsychotic medication discontinuation has recently been acknowledged by the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) [20]. However, to close the gap between experimental clinical research and routine practice, open-label, non-randomised studies are also required. Early observational designs involving second-generation antipsychotics did not focus on treatment maintenance and the factors influencing it in everyday care [4,10,18]. In contrast, the study by Ascher-Svanum et al. was specifically designed to evaluate time to antipsychotic discontinuation under routine clinical practice, but it has not been performed on European patients [2].

The Schizophrenia Outpatient Health Outcomes (SOHO) study was designed to provide clinician-acknowledged data and addressed, among others, the issue of treatment durability. This study involved more than 10,000 patients across Europe of which approximately one-fifth were recruited and followed up in Spain. The objectives of this article are (1) to provide data on treatment discontinuation in schizophrenia and (2) to describe the correlates of 3-year antipsychotic maintenance in the actual outpatient setting specific for Spain.

2. Methods

2.1. Design of the study

The SOHO was a prospective, open-label, 3-year, observational, pan-European study of the treatment of schizophrenia with specific focus on olanzapine and, within Spain, that involved 86 psychiatrists who evaluated 2020 patients in total.

Enrolment was offered to patients aged at least 18 years initiating or changing antipsychotic medication for schizophrenia presenting as outpatients within their routine care. There were no restrictions for enrolment regarding either the type of antipsychotic medication prescribed, the type of therapeutic action (initiation of treatment, replacement for previous medication or addition to existing treatment) or the reason for treatment change (lack of response, side effects, etc.). Patients treated with antipsychotics for reasons other than schizophrenia were not included.

Since the initial objective of SOHO was to compare olanzapine with other antipsychotics, 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. The olanzapine group was over-sampled and thus it does not reflect its actual prescription. Interestingly, although a systematic alternating order to recruit patients between the two cohorts was used to achieve this in most countries, within Spain investigators were not required to respect the alternating sequence, but to enrol a similar number of patients in each cohort. To avoid interference with routine practice to the maximum extent, psychiatrists were not compelled to recruit a minimum of patients to participate, the recruitment period was intentionally long, and they were instructed to make treatment decisions before and independently from assessing patients for enrolment. No instructions about patient care were included in the study description. All patient care was at the discretion of the participating psychiatrist.

All the regional Ethics Committees involved approved the study prior to commencement and a written informed consent was obtained from each participant at enrolment.

2.2. Study assessments

The baseline data was collected at the routine visit at which patients were enrolled. The intention was to obtain data at 3, 6 and every 6 months afterwards until the completion of the 3-year follow-up. To minimise the impact on routine clinical practice, a 2-month time window was allowed around target months. If a routine visit did not take place within 1 month before or after the target month, the corresponding assessment was left blank.

Outcomes in terms of clinical severity and social functioning were assessed. For the clinical severity, a scale based on the Clinical Global Impression (CGI) scale which evaluated overall, positive, negative, cognitive and depressive symptoms during the week preceding the day of the assessment was used [15]. Social functioning was assessed with single-item questions that asked whether the patient was involved in any social interaction in the preceding 4 weeks (socially active), had paid employment, a relationship with spouse or partner, or was exhibiting verbal or physical hostile or aggressive behaviours.

In addition, psychiatrists collected information on the medication that was prescribed to the patient. In particular, a thorough record of the antipsychotics that the patient was taking before and that were prescribed at each visit was made. Reasons for medication change were also recorded and classified as lack of efficacy, intolerance, lack of compliance or patient request. The outcome analysed for this report is the lack of medication changes over the follow-up (medication maintenance).

2.3. Statistical analyses

In addition to the olanzapine and non-olanzapine groups, treatment cohorts were defined according to the antipsychotic initiated at the baseline assessment based on the following categories: olanzapine (corresponding to the olanzapine group), risperidone, quetiapine, clozapine, any oral typical antipsychotic, and depot typical antipsychotic. The post-hoc analyses reported here considered only those patients on monotherapy at the start of the study, which includes those who discontinued their pre-study medication by down-titration before the 3-month visit.
Treatment discontinuation was defined at each visit as the interruption, replacement or addition of a new antipsychotic drug to the antipsychotic initiated at baseline treatment. The time to all-cause treatment discontinuation was described by means of the Kaplan–Meier method. For medication changes that occurred at assessment visits, the time of medication discontinuation used in the survival analyses was the month of the visit. For medication changes that occurred between two visits, the time of medication change was the mean time between the visits. It could be possible that, in between visits, a patient could change medication and come back to the previous medication before the following visit. These medication changes were not detected.

In addition, the risk of discontinuing the baseline treatment for any reason throughout the 3-year follow-up period was modelled by means of the Cox proportional-hazards method accounting for the following baseline data: antipsychotic drug initiated with olanzapine as the reference cohort; age, age at first treatment contact, time since first treatment contact, body mass index, the overall, positive, negative, depressive and cognitive CGI-SCH score; and the dichotomous variables (a) gender, (b) presence of stable partner, (c) any social relationship in the prior 4 weeks, (d) paid employment, (e) presence of significant extrapyramidal symptoms, (f) current substance abuse, (g) current alcohol abuse, (h) whether the patient was in the first treatment for schizophrenia, (i) presence of hostile behaviour, whether the patient received concomitant prescription of (j) anticholinergics, (k) antidepressants, (l) anxiolytics/hypnotics, (m) mood stabilisers, and the reasons for change of pre-baseline treatment classified as either (n) lack of effectiveness, (o) intolerability, (p) lack of compliance, (q) patient’s request. Four further models were adjusted with the same independent variables for each of the different reasons for discontinuation as well: lack of effectiveness, intolerable side effects, lack of compliance and patient’s request. In the final models presented here, only those independent variables that remained after performing a stepwise model reduction were kept.

There was no calculation of the size of the sample used in these analyses because they are regarded as a subgroup of patients from the parent study. Neither was any adjustment for multiple comparisons considered because the consideration of independent variables in the multivariate techniques employed was defined a priori based on prior knowledge of factors affecting compliance on routine clinical setting and independent of the results obtained in the analyses.

3. Results

3.1. Characteristics of the sample

Of the 2020 patients recruited and followed in Spain, 1688 (83.6%) started treatment with only one antipsychotic treatment after the baseline visit. Of these, 950 (56.2%) initiated treatment with olanzapine; and the remaining 738 (43.7%) formed the control group. Within the control group, the risperidone cohort was the most numerous (404 patients, 23.9%), followed by quetiapine, oral typical, depot typical antipsychotics and clozapine.

Table 1 shows the demographic and clinical characteristics of the patients on monotherapy at the start of the study by the antipsychotic started at baseline. The majority of patients were male (more than one-half), had a mean age at baseline of approximately 40 years and the time since the diagnosis of schizophrenia of 11 years. Almost one-tenth (159 patients, 9.4%) were antipsychotic naïve. Patients in the clozapine cohort were on average younger (30.6 years), had a shorter time since diagnosis (8.6 years) and were more severely ill (as shown by the higher CGI scales scores) than patients starting other medications. The reason for the change of prior antipsychotics was lack of compliance in a greater proportion of patients that started treatment with depot typical antipsychotics than among patients starting other medications.

Of the 1688 patients included in the analyses, 1175 (69.6%) have been evaluated at 3 years. Logistic regression analysis revealed that patients starting treatment with quetiapine had a lower chance of completing follow-up than patients starting olanzapine (odds ratio (OR) 0.65; 95% confidence interval (CI) 0.45–0.94). Being socially active in the 4 weeks before baseline (OR 1.30; 95% CI 1.02–1.66) was associated with completing follow-up.

Table 2 shows the mean medication doses by atypical antipsychotic at baseline and at 3 years and the use of concomitant medications at baseline. The doses of atypical antipsychotics were within the recommended ranges. The prescription of concomitant medications at baseline, especially of anxiolytics/hypnotics was high. The proportion of patients that were prescribed anticholinergics at baseline was greater in the risperidone and typical antipsychotics groups than in the remaining cohorts.

The longest time to treatment discontinuation corresponded to patients in the clozapine cohort, followed by patients in the olanzapine and risperidone cohorts (the upper lines in Fig. 2). The estimated proportions of patients that maintained the treatment throughout the 3-year period were, in these cohorts, 78.9%, 66.9% and 60.6%, respectively. The shortest time was found among patients receiving quetiapine or an oral typical antipsychotic (Fig. 2); the respective estimated proportions of maintenance were 30.9% and 38.8%.

The adjusted analyses of medication discontinuation for any reason revealed that some variables were associated with a greater or lower chance of treatment maintenance (Fig. 1); the type of antipsychotic medication prescribed at baseline was an important predictor. Patients who started risperidone, quetiapine, an oral typical, or a depot typical antipsychotic had a significantly greater risk of discontinuation (or the time to treatment discontinuation was significantly shorter) than those on olanzapine (p-values: 0.015, <0.001, <0.001 and 0.001, respectively). Those who started on clozapine were at lower risk than those on olanzapine, although this difference did not reach statistical significance (p-value: 0.309).

Other predictors of treatment maintenance were also identified (Fig. 1). Patients who took mood stabilisers, patients with a higher (worse) score in the CGI-SCH cognitive scale, and
patients with a greater body mass index at baseline were at significantly higher risk (p-values: 0.010, 0.021 and 0.001, respectively). Conversely, those engaged in social activities were at lower risk (p-value: 0.020) of discontinuing treatment throughout the 3-year follow-up. A marginal association was also found of longer duration of the illness with lower risk of discontinuation (the longer the duration, the lower the risk; p-value: 0.057).

Overall, the analyses of medication discontinuation for specific reasons yielded results similar to the analysis of discontinuation for any reason (Table 3).

### 4. Discussion

The 3-year results on treatment discontinuation within Spain are in general consistent with the 1-year [16] and 3-year [17] results in the whole sample of the SOHO; albeit statistical significance was attenuated because loss of power with the reduced sample size. Comparison with the results of the Intercontinental SOHO (IC-SOHO) [7–9], a similar study that is being performed in other populations including Asia, Australia and Latin America, is not possible at this time because long-term treatment discontinuation data from the latter study are not available.
not available yet. The proportions of patients that remained in the same treatment prescribed at baseline were almost threefold lower after 3 years than after 1 year, indicating that the discontinuation rate remained constant during the second and third years of follow-up. More importantly, the relative differences among the antipsychotics were similar after 3 years than after the first year, supporting the notion that the type of antipsychotic prescribed is a key predictor of medication maintenance. Clozapine was the drug that showed the highest frequency of maintenance, which is consistent with previous reports [25]; although the results in this cohort should be considered with caution because the group of patients to whom clozapine is prescribed (refractory patients who are more closely monitored) might differ qualitatively from patients receiving any other antipsychotics. The proportions of patients that discontinued treatment were significantly lower in the olanzapine and clozapine cohorts than in the remaining cohorts. This is a striking long-term result for olanzapine because, as mentioned, antipsychotic adherence is a major contributor for therapeutic outcome. The recently reported results from the CATIE study have also shown a more favourable outcome with olanzapine in terms of treatment maintenance [20]. Of note is that in the present study all patients had been switched to a new medication, corresponding to the CATIE subgroup analysed by Essock et al. in which results were blunter than in the whole sample [12]. In this vein, these SOHO results may support the notion that the likelihood of success of antipsychotic switching is greater when done on clinical grounds than by randomisation. Although the reasons for improved compliance with antipsychotic medication are controversial, higher efficacy [6], improved tolerability and a sound therapeutic alliance between physician and patient

Fig. 1. Hazard ratios and 95% confidence limits of the covariates used in the Cox proportional hazards model of the time to all-cause treatment discontinuation. Intervals lying entirely at the right of the dotted line indicate a significantly greater risk of discontinuation for the first (exposed cases) versus the second condition (unexposed cases) or with the change in the sense indicated in ordinal variables (marked with an asterisk) and vice versa.

Fig. 2. Survival distribution function of the time to all-cause treatment discontinuation by treatment cohort.
Table 3
Hazard ratios of factors associated with discontinuation of initial antipsychotic medication owing to lack of effectiveness, intolerable side effects, lack of compliance and patient’s request throughout the 3 years of follow-up

<table>
<thead>
<tr>
<th>Factor</th>
<th>Any reason</th>
<th>Lack of effectiveness</th>
<th>Intolerability</th>
<th>Lack of compliance</th>
<th>Patient’s request</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Greater) time since first contact&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.999</td>
<td>0.99–1.00</td>
<td>0.999</td>
<td>0.99–1.01</td>
<td>0.996</td>
</tr>
<tr>
<td>Gender (female vs. male)</td>
<td>0.949</td>
<td>0.80–1.13</td>
<td>1.151</td>
<td>0.90–1.47</td>
<td>0.742</td>
</tr>
<tr>
<td>(Greater) baseline body mass index&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.029</td>
<td>1.01–1.05</td>
<td>—</td>
<td>—</td>
<td>1.048</td>
</tr>
<tr>
<td>(Greater/worse) baseline overall CGI score&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.007</td>
<td>0.91–1.21</td>
<td>1.175</td>
<td>1.03–1.34</td>
<td>0.961</td>
</tr>
<tr>
<td>(Greater/worse) baseline positive CGI score&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(Greater/worse) baseline negative CGI score&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>1.258</td>
</tr>
<tr>
<td>(Greater/worse) baseline depressive CGI score&lt;sup&gt;a&lt;/sup&gt;</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>(Greater/worse) baseline cognitive CGI score&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.106</td>
<td>1.02–1.21</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Social activities at baseline (yes vs. no)</td>
<td>0.804</td>
<td>0.67–0.97</td>
<td>0.700</td>
<td>0.54–0.90</td>
<td>—</td>
</tr>
<tr>
<td>Paid employment at baseline (yes vs. no)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Use of concomitant mood stabilisers (yes vs. no)</td>
<td>1.499</td>
<td>1.10–2.04</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Use of concomitant antidepressants (yes vs. no)</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Extrapyramidal symptoms baseline (yes vs. no)</td>
<td>—</td>
<td>—</td>
<td>1.323</td>
<td>1.04–1.69</td>
<td>—</td>
</tr>
<tr>
<td>Treatment changed for lack of effectiveness (yes vs. no)</td>
<td>—</td>
<td>—</td>
<td>1.512</td>
<td>1.19–1.93</td>
<td>—</td>
</tr>
</tbody>
</table>

**Antipsychotic prescribed at baseline (cohort)**

| Risperidone vs. olanzapine | 1.297 | 1.05–1.60 | 1.461 | 1.08–1.98 | 1.366 | 0.86–2.18 | 1.674 | 1.07–2.63 | 1.019 | 0.68–1.52 |
| Quetiapine vs. olanzapine | 2.742 | 2.13–3.53 | 3.956 | 2.83–5.54 | 2.407 | 1.34–4.32 | 3.962 | 2.29–6.86 | 1.758 | 1.01–3.06 |
| PO typical vs. olanzapine | 2.102 | 1.50–2.95 | 2.836 | 1.78–4.53 | 2.812 | 1.41–5.62 | 2.845 | 1.38–5.86 | 1.865 | 0.97–3.60 |
| Depot typical vs. olanzapine | 1.816 | 1.27–2.60 | 3.095 | 1.97–4.86 | 1.340 | 0.53–3.36 | 1.190 | 0.43–3.33 | 1.129 | 0.49–2.60 |
| Clozapine vs. olanzapine | 0.656 | 0.29–1.48 | 0.636 | 0.20–2.01 | 0.122 | 0.27–4.64 | 0.502 | 0.07–3.66 | 0.717 | 0.18–2.93 |

**HR**, hazard ratio of medication discontinuation; CI, confidence interval.

<sup>a</sup> Relative frequencies have been calculated over the total of available cases for each variable that sometimes was lower than the group total, n.

[5,13] have been shown to contribute. Additionally, longer maintenance was associated with higher social abilities and better cognitive status at baseline (this latter result was not found after 1 year). Albeit the cognitive CGI-SCH scale was not conceived to specifically address the level of insight, this finding supports previous reports that improved insight may enhance compliance [11,21]. On the other hand, and consistently with other reports [26], we have not found any relationships between demographic factors and illness history on antipsychotic medication maintenance. The greater risk of treatment discontinuation of patients who received mood stabilisers concomitantly compared to those that did not may be the result of a more complex clinical condition, with greater severity, comorbidities and difficulties with pharmacotherapy in poly-medicated patients because of adverse events or drug-drug interactions.

In contrast with the aforementioned results in the whole sample after 1 year, patients in the Spanish sample who were never treated with antipsychotics for schizophrenia before baseline did not have a greater risk of discontinuation than non-naive patients. This is a particular finding of this analysis, and may indicate that, within Spain, in contrast to what occurs in other European countries, more dedicated care is delivered to newly diagnosed cases of schizophrenia, which may compensate for the initial reluctance of patients and families to accept the diagnosis and the treatment.

It is worth noting that the average daily doses of atypical antipsychotics reported in this study are those that treating psychiatrists chose on the basis of their clinical practice patterns. Thus, the concerns about limited drug performance caused by restrictions to dosing in experimental studies would not operate in this study. Nevertheless, this might not be the case with quetiapine, because of its recent introduction and the limited therapeutic experience that clinicians had with it by the time the patients were recruited, when more recent reports relating greater efficacy to higher doses [3] were not available. This could be a factor in its worse performance with respect to other antipsychotics. The clozapine dose also deserves some comment because it was also low; probably indicating the avoidance of patients with severe treatment-resistant schizophrenia in the study.

This study has some limitations that have to be considered when judging maintenance results. First, it was not the primary objective and thus there may be some unobserved covariates that could be influencing the results. On the other hand, the rate of medication maintenance in the SOHO study may be somewhat higher than in the actual clinical setting, as investigators may have tended to include compliant patients. This selection bias, however, would not affect the comparison between cohorts. The larger size of the olanzapine cohort, though reinforcing the relevance of the lack of differences with clozapine, may magnify the differences with other drugs as well. This is especially relevant in the case of risperidone, with which the statistical superiority was only marginal. As in the case of the analyses of remission and relapse, the presence of information biases cannot be discarded, as participating psychiatrists were not blinded to treatment. However, in this case such bias is less plausible since the endpoint evaluated (medication maintenance/change) was not based on subjective assessment by the clinician.
5. Conclusion

In conclusion, the SOHO study provides an excellent frame to evaluate the effectiveness of antipsychotics in the treatment of schizophrenia in terms of long-term maintenance. The results presented refer specifically to patients recruited and treated within Spain; and, although there were certain particularities, they are rather consistent with what was observed in the whole sample of the study. The most prominent finding is that differences in effectiveness do exist between antipsychotics. This stresses the importance of a careful drug selection to best fit the individual patient’s needs. Clozapine and olanzapine were the drugs most effective in terms of treatment discontinuation. Possible selection and information biases derived from the non-systematic, non-randomised allocation to treatments and the existence of unobserved covariates may influence the outcome should be considered when considering these conclusions.

References


