COMMENTARY

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The SOHO (Schizophrenia Outpatient Health Outcome) Study

Implications for the Treatment of Schizophrenia

Josep Maria Haro[1] and *Luis Salvador-Carulla*[2]

1 Sant Joan de Déu-SSM, Fundació Sant Joan de Déu, Sant Boi de Llobregat, Barcelona, Spain
2 GEMP, Universidad de Cádiz, Cádiz, Spain

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Abstract

The European SOHO (Schizophrenia Outpatient Health Outcome) study is an observational, naturalistic study of the outpatient treatment of schizophrenia. The patient recruitment and assessment began in September 2000 and finished in early 2005. A total of 10 972 adult patients from ten European countries who were initiating or changing antipsychotic medication for the treatment of schizophrenia within the normal course of care have been enrolled. The patients have been followed at regular intervals over the 3-year timeframe of the study. Evaluation includes clinical severity, measured with the Clinical Global Impression (CGI) scale; health-related quality of life; social functioning; and medication tolerability.

The 6- and 12-month results have been published so far and have demonstrated that the patients in whom treatment was initiated with olanzapine or clozapine or who were started on more than one antipsychotic of any class at baseline tended to have somewhat greater improvement than patients treated with other atypical or typical antipsychotics, both in terms of symptoms measured with the CGI and quality of life. Numbers of social contacts increased with the treatment, but other aspects of social functioning did not show any significant change.

Atypical antipsychotics as a class were associated with a lower frequency of extrapyramidal symptoms (EPS) and anticholinergic use than typical antipsychotics. The frequency of EPS was lowest in the clozapine-, quetiapine- and olanzapine-treated patients, at around 10%. The atypical antipsychotics also conferred a lower risk for tardive dyskinesia than the typical antipsychotics. Weight gain occurred in all treatment cohorts over the first 12 months of treatment and was statistically significantly greater in the patients who started treatment

with olanzapine and clozapine. Prolactin- and sexually-related adverse events were frequent at baseline assessment: amenorrhoea was present in around one-third of women, impotence in around 40% of men, and loss of libido in 50% of both male and female patients. Patients treated with olanzapine, clozapine and quetiapine were significantly less likely to have sexual/endocrine-related dysfunctions after 6 months of treatment (the 12-month results of this parameter are yet to be published) than those in the other treatment cohorts (typical antipsychotics, risperidone and amisulpride). Concomitant medication use during the study has been high, ranging from 5% to 29% for anticholinergics, 8% to 23% for antidepressants, 22% to 37% for anxiolytics and 7% to 19% for mood stabilisers, depending on the type of antipsychotic prescribed. Fewer olanzapine-, quetiapine- and clozapine-treated patients used concomitant anticholinergics or anxiolytics/hypnotics.

The current results from the SOHO study indicate that differences in effectiveness and tolerability do exist between the antipsychotics. Future results from the study will be published during the coming months and years, and will allow patterns of antipsychotic use in routine clinical practice (including how often and why changes are made) to be determined. This important information is likely to impact on the future use of antipsychotics and will assist clinicians in refining the use of these drugs and improving the outcome of patients to whom they are prescribed.

1. Background to the SOHO Study

Since the introduction of antipsychotic drugs, pharmacological treatment has been the cornerstone of the management of schizophrenia. 'Classical' or 'typical' antipsychotics, like haloperidol, are very effective in treating positive symptoms, but only 70% of patients respond to these agents[1,2] and at least 15–20% of patients relapse each year.[3,4] Furthermore the influence of these drugs on negative symptoms and cognitive performance is still a matter of debate.[5-8] The adverse effect profile of typical antipsychotics continues to be an important hindrance to their use that affects compliance and limits effectiveness.[9]

The last three decades have seen the appearance of the so-called 'second generation' or 'atypical' antipsychotics (clozapine, risperidone, olanzapine, quetiapine and sertindole, among others). These medications have a different adverse effect profile to the typical antipsychotics[10,11] and have been found to be as effective in reducing the positive symptoms of schizophrenia.[10,12,13] Atypical antipsychotics appear to decrease negative symptoms to a greater extent than the typical agents,[14] either by reducing secondary negative symptoms or by a direct effect on the primary negative symptoms. It has also been claimed that atypical antipsychotics have a beneficial effect on cognitive functioning,[15,16] which may be explained in part by the fact that the concurrent use of anticholinergic drugs (which can negatively affect cognitive functioning) is not required.[17] Most recent guidelines on the treatment of schizophrenia consider these newer agents (except for clozapine because of its potential risk of agranulocytosis) to be first-line choices for the treatment of the disorder, despite their higher price.[18-21]

Most of the current knowledge about the effects of antipsychotics in the treatment of schizophrenia comes from randomised clinical trials (RCTs), which are considered to be the gold-standard for testing the effect of new treatments. However, such trials are conducted under controlled circumstances, and this poses important limitations in translating the findings to common practice. Clinical trials are usually conducted in academic centres that yield only a partial representation of the people who have

schizophrenia and their respective treatment. These trials impose stringent inclusion and exclusion criteria to augment consistency of the experimental groups and increase the internal validity of the study. Hofer et al.[22] have estimated that only approximately 20% of patients are eligible for inclusion in clinical trials.

The SOHO (Schizophrenia Outpatient Health Outcome) study, an observational, naturalistic study of the outpatient treatment of schizophrenia, was designed to complement results from clinical trials, by providing information on antipsychotic treatment effects in day-to-day clinical practice. Although naturalistic studies of the treatment of schizophrenia have been conducted previously, most are limited in their ability to evaluate all the variability associated with schizophrenia because they had short follow-up periods, included small numbers of patients or used limited measurement parameters.

2. Description of the SOHO Study

The SOHO study has been conducted in ten European countries. The patient recruitment and assessment began in September 2000 and finished in early 2005. 1096 investigators have participated and have enrolled at least one patient. The investigators were psychiatrists working mostly in public (46.9%) or combined public and private (37.2%) practices.[23] A total of 10 972 patients were recruited.

Recruitment was highest in Germany (3449 patients), Italy (3016 patients) and Spain (2053 patients). The remaining 2454 patients were enrolled in Denmark, France, Greece, Ireland, The Netherlands, Portugal and the UK. 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.

Participating psychiatrists offered enrollment to outpatients, at least 18 years of age, who were initiating or changing antipsychotic medication for the treatment of schizophrenia within the normal course of care. The study was designed to provide two patient cohorts of approximately equal size: patients who initiated therapy with or changed to olanzapine; and patients who initiated therapy with or changed to a non-olanzapine antipsychotic. The main objective of the study was to compare the outcomes of patients initiating olanzapine with those of patients initiating other antipsychotic medications. A total of 10 972 patients were recruited, of which 1033 had never previously been treated with antipsychotics. The study has been promoted and funded by Eli Lilly and Co., and the investigators were paid by the company for the time spent collecting data.

Effort was made to avoid interference with clinical practice. Investigators were instructed to make treatment decisions independent of the study and then evaluate whether patients were eligible for inclusion based on entry criteria and the structure of enrollment. The recruitment period was purposely very long and no minimum number of cases was required per investigator. All patient care was at the discretion of the participating psychiatrist; no instructions about patient care were included in the study description. 5376 patients started on olanzapine at baseline visit, 1918 started on risperidone and 790 on quetiapine. The figures for the rest of the antipsychotics were 328 for amisulpride, 327 for clozapine, 688 for oral typical antipsychotics and 485 for depot typicals. 268 patients started on more than one antipsychotic at baseline.

Patients have been evaluated over a 36-month period post-baseline. Evaluations were targeted for 3 months, 6 months and then every 6 months up to 36 months after baseline. Evaluation was allowed to occur in an interval 1 month around the target evaluation date. Patients who were not seen during the normal course of care within one assessment interval are not excluded from subsequent data collection.

Four types of outcome were assessed in the study: clinical severity, health-related quality of life, social functioning and tolerability. Clinical severity was assessed using a scale based on the Clinical Global Impression (CGI) scale,[24] which evaluated positive, negative, cognitive, depressive and overall symptoms on the day of assessment. This scale was expanded and later validated as the Clinical Global Impression-Schizophrenia scale (CGI-SCH).[25]

Quality of life was assessed using the EuroQol-5 Dimensions (EQ-5D), a patient self-rated, generic, health-related quality-of-life instrument. Social functioning was assessed using single-item questions about the patient's social interactions, employment, relationship with a partner, and verbal or physical hostile or aggressive behaviours. Extrapyramidal symptoms (EPS), tardive dyskinesia, loss of libido, amenorrhoea/menstrual disturbances, gynecomastia, impotence/sexual dysfunction and galactorrhoea were evaluated by the participating investigators.

3. What Can the SOHO Study Add to Our Knowledge of the Treatment of Schizophrenia?

It is hoped that the size and duration of the SOHO study will produce a diversity of results. Firstly, the study may provide information on the patterns of treatment for schizophrenia in the outpatient setting (which drugs are used most frequently, at what dosages, in which combinations). Secondly, information should be obtained about outcomes in outpatient treatment, in terms of clinical effectiveness, tolerability, quality of life and social functioning. Finally, the rich dataset may also be used to analyse many aspects of schizophrenia that are not directly related to medication treatment, such as sex differences in the course of the disorder, determinants of social functioning or country differences in patterns of care.

Results from the 6- and 12-month assessment intervals have already been published or are in press.[26-29] The rest of the present article will summarise the main findings from the SOHO study, compare them with the existing literature, and comment on new lines of research that the study can pursue.

Patients were included in the SOHO study because they required an antipsychotic medication (the initiation of a first antipsychotic or the change from one antipsychotic to another) for clinical reasons, most frequently a lack of effectiveness of previous medication but also intolerance to the previous medication or patient request. Most of the patients included improved after the medication change, and what the analysis has focused on is the factors that are associated with that improvement. The improvement observed during the first 6 and 12 months has been seen in clinical symptoms, medication adverse effects and self-perceived quality of life. The number of social contacts also improved, but other aspects of social functioning (relationship with a partner, working or living independently) did not show any significant changes.

The 6- and 12-month analysis also showed that some treatments are associated with a slightly better outcome than others. Patients who initiated treatment with olanzapine or clozapine or who were started on more than one antipsychotic of any class at baseline have tended to have somewhat greater improvement than patients treated with other atypical or typical antipsychotics, both in terms of symptoms measured with the CGI scale and quality of life.[26]

These results confirm the previously reported findings of a greater effectiveness of clozapine compared with other antipsychotics[30] and provide support for using combinations of antipsychotics. Combination therapy with more than one antipsychotic is frequent in clinical practice, but very few clinical trials have been conducted to evaluate it.[31] The finding of greater improvement in the patients who started olanzapine compared with typical antipsychotics, risperidone, quetiapine and amisulpride is, however, controversial. Most studies and reviews have not found a better outcome with olanzapine compared with typical and other atypical antipsychotics,[32-36] and a recent well designed clinical trial did not find olanzapine to be more effective than haloperidol.[37] Some studies, on the other hand, have suggested that clozapine and olanzapine are similarly effective, particularly in patients with treatment-resistant schizophrenia,[38,39] and that olanzapine may be more effective than risperidone[40] or typical agents[12,41] The recently published CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) trial also found olanzapine to be more effective than risperidone, quetiapine, ziprasidone and perphenazine.[42]

Some factors may explain the difference in the results of the SOHO study compared with those of clinical trials and its consistency with the results of the CATIE trial. Firstly, the differences favouring olanzapine in the SOHO study have been of a small magnitude and it could be that only large studies such as the SOHO study can capture these small differences. Secondly, the SOHO study has had a much higher retention rate than clinical trials. Wahlbeck et al.[43] found that dropout rates from clinical trials were around one-third, while in the SOHO study the 1-year retention rate was around 85%. Thirdly, the outcomes of the SOHO study depend not only on antipsychotic efficacy but also on other factors such as medication compliance and adverse effect profile. However, although the design and analysis of the SOHO study have included several strategies to avoid and control biases, it cannot be ruled out that the results are partially or completely explained by biases that were not controlled; new observational studies are needed to confirm these findings.

The 6-month results that indicated better clinical outcomes with olanzapine and clozapine were confirmed in the 12-month analysis, which showed that these medications were associated with greater medication adherence than other atypical (risperidone, quetiapine, amisulpride) and the typical antipsychotics.[44] These results confirm the findings from the CATIE trial that patients treated with olanzapine remained on that medication for longer than patients treated with risperidone, perphenazine, quetiapine or ziprasidone.[42]

The SOHO study has also provided information about treatment-emergent adverse events. In the study, atypical antipsychotics as a class have been associated with a lower frequency of EPS and anticholinergic use than typical agents. The frequency of EPS was lowest in the clozapine-, quetiapine- and olanzapine-treated patients, with a frequency of around 10%. In a meta-analysis of RCTs, patients treated with olanzapine, quetiapine, risperidone and sertindole used less antiparkinsonian medication than haloperidol-treated patients.[45] In SOHO, risperidone-treated patients have shown a greater frequency of EPS compared with patients receiving other atypicals, which is consistent with previous reports.[46] Anticholinergic use in the typical antipsychotic groups (oral and depot) was high compared with the risperidone group, which may indicate that EPS in the former groups are more severe than in risperidone recipients. EPS are a relevant clinical outcome, since they are associated with treatment non-adherence, dropouts and the use of concomitant medications, especially anticholinergics.[47,48] Patient adherence, therefore, may be improved by switching to an atypical antipsychotic that produces fewer EPS, reducing the need for antiparkinsonian medication.[49]

The SOHO study also has shown that atypical antipsychotics confer a lower risk for tardive dyskinesia than typical antipsychotics, which reinforces the view that the relative advantage of atypical agents in terms of lower rates and persistence of tardive dyskinesia that was in observed in RCTs generalises to routine clinical care.[50] SOHO has also showed that EPS is a predictor of later tardive dyskinesia, providing opportunities for risk reduction in the population exposed to antipsychotics.[51]

Weight gain occurred in all treatment cohorts over the first 12 months of treatment, and it was statistically significantly greater in the patients who started treatment with olanzapine and clozapine. Weight gain, as an adverse event of antipsychotic medications, may contribute to the increased risk for obesity-associated problems in patients with schizophrenia.[52,53] The findings of the SOHO study are in agreement with a meta-analysis by Allison et al.,[54] which revealed that, among the antipsychotics, clozapine and olanzapine were associated with the greatest weight gain after 10 weeks of treatment. However, differences in weight gain between the olanzapine and clozapine cohorts and the other treatment cohorts in the SOHO study have been small (around 1.3kg during the first 6 months of treatment, lower than in previous reports).[55] Most of the weight gain occurred in the first 3 months of treatment.[27]

Prolactin- and sexually-related adverse events are also frequently found in patients being treated

for schizophrenia.[56] At the baseline assessment for the SOHO study, amenorrhoea was present in around one-third of women, impotence in around 40% of men, and loss of libido in half of the male and female patients.[27] Patients treated with olanzapine, clozapine and quetiapine were significantly less likely to have sexual/endocrine-related dysfunctions after 6 months of treatment (the 12-month results are yet to be published) than those in the other treatment cohorts (typical antipsychotics, risperidone and amisulpride). These findings are consistent with reports from clinical studies that olanzapine and quetiapine are associated with less sexual dysfunction than risperidone or typical antipsychotics.[57,58] The mechanisms underlying sexual and endocrine dysfunctions in antipsychotic-treated patients are poorly understood but may be related to increased prolactin levels.[59]

Medication dosage is an important modifier of medication effects and the results outlined above should be considered in light of the dosages the patients were taking.[36] The antipsychotic dosages used in the SOHO study are consistent with those from previous studies, clinical experience and pharmacological guidelines for schizophrenia. The mean dosages of olanzapine (11.95 and 11.91 mg/day),[60] risperidone (4.91 and 4.92 mg/day),[55] amisulpride (mean 401.20 and 428.83 mg/day)[61] and quetiapine (mean 382.53 and 383.70 mg/day)[62] at 6 and 12 months were similar to those recommended for the treatment of schizophrenia. The dose titration took longer with quetiapine than for other treatments, which could be explained by the fact that quetiapine was a relatively recently launched drug when SOHO was initiated. A detailed analysis of dosage has not yet been undertaken in the SOHO study.

Using data from the SOHO study, Novick et al.[29] examined the use of psychotropic medication besides antipsychotics. Concomitant medications are widely used in the treatment of patients with schizophrenia,[63] but their use remains a debatable issue and there is little scientific evidence to support the clinical utility of this approach.[64] The use of concomitant medications in the SOHO study has been high, ranging from 5% to 29% for anticholinergics, 8% to 23% for antidepressants, 22% to 37% for anxiolytics and 7% to 19% for mood stabilisers, depending on the type of antipsychotic prescribed.[29] Some antipsychotics were associated with less use of concomitant medication. Olanzapine, clozapine and quetiapine were associated with less use of anticholinergics than risperidone and typical antipsychotics. Olanzapine, depot typical antipsychotics and amisulpride were associated with less use of anxiolytics than risperidone and oral typical antipsychotics. The results are consistent with previous studies, which reported that olanzapine-treated patients used fewer anticholinergics than those taking other antipsychotics[65,66] and that atypical antipsychotics in general were associated with significantly less use of concomitant anticholinergics and anxiolytics than typical antipsychotics.[67] Females enrolled in the SOHO study have used more concomitant medication than males, especially antidepressants, which is consistent with the higher frequency of affective and anxiety symptoms in women.[68]

The sample size of the SOHO study allows the detailed analysis of patient subgroups. Gasquet et al.[28] have published the 6-month outcomes of the >1000 patients who, before inclusion in the study, had never before been treated with antipsychotics. The results in general replicate the analysis of the main SOHO group. The analysis of this cohort of patients at 3 years will provide an excellent source of information regarding treatment for patients with first-onset schizophrenia.

4. Methodological Considerations in the Analysis and Interpretation of Results from the SOHO Study

The SOHO study is a non-randomised, observational study that is intended to capture what happens in usual clinical practice. Some issues need to be taken into account when analysing and interpreting the results. Firstly, direct comparisons between the medication groups are not appropriate since psychiatrists in routine clinical practice prescribe different medications to different patients, trying to maximise their potential benefits. In order to adjust for these

differences between patients, statistical models that adjust for confounders have been used in all analyses of the data from the study. This review has only focused on the results provided by these analyses. Previous research has found that when observational studies have appropriate designs and analysis strategies, comparisons of the findings of RCTs and observational studies reveal no major differences in the effects of treatments.[69]

Secondly, approximately half of the patients in the SOHO study started therapy with olanzapine, due to the study design. Oversampling of the olanzapine cohort was included in the study protocol because the main objective of the study was to compare olanzapine with other antipsychotics; however, this may have some implications. The sample of patients included in the study was not directly representative of the population of patients starting a new antipsychotic in the outpatient setting; however, this limitation may not be relevant when studying the longitudinal effects on patients who start each medication. Besides, the effect of having a large sample of patients taking olanzapine is the ability to obtain very precise estimates of the outcomes of this group. For treatment groups where the number of patients is small, the precision of the estimates obtained is reduced.

The important strengths of the SOHO study also deserve highlighting. Firstly, there has been a high retention rate, much higher than that seen in RCTs where high dropout rates can limit the drawing of firm conclusions. Secondly, patients can change medication at any point and still remain in the study and be evaluated, which allows for the study of a number of issues that cannot be studied in standard clinical trials.

5. Conclusion

The SOHO study is, to our knowledge, the largest study of the treatment of schizophrenia published to date. It will provide an enormous wealth of information on the outpatient care of schizophrenia. Some analyses from the first 6 and 12 months of the study have already been published. These analyses show that dosages of prescribed medications in outpatient care are within the recommended ranges, that differences in effectiveness among antipsychotics do exist and that tolerability also varies among treatments.

In the coming months and years, many more results from the SOHO study will become available. The 3-year data will allow the investigation of new issues, such as the patterns of antipsychotic treatment, how often and why patients change medication, and how this impacts on outcome.

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Correspondence and offprints: Dr *Josep Maria Haro*, Sant Joan de Déu-SSM, Fundació Sant Joan de Déu, Dr. Antoni Pujadas 42, 08830 – Sant Boi de Llobregat, Barcelona, Spain. E-mail: jmharo@fsjd.org