Use of concomitant medication with antipsychotic treatment in outpatients with schizophrenia: Results from the European Schizophrenia Outpatients Health Outcomes (SOHO) study

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Abstract

Use of concomitant medications with antipsychotic agents in the treatment of schizophrenia is common but lacks a clear scientific rationale. We evaluated concomitant medication usage during the first 6 months of the prospective, observational, European Schizophrenia Outpatient Health Outcomes (SOHO) study, examining its frequency, variation according to type of antipsychotic drug used, and impact on treatment tolerability. We also determined factors that were associated with concomitant medication use. The use of concomitant medications differed greatly among the countries participating in the SOHO study. The presence of depressive symptoms and being female were associated with the use of concomitant antidepressants. Certain antipsychotics were associated with less use of concomitant medications: significantly fewer olanzapine-, quetiapine- and clozapine-treated patients used concomitant anticholinergics or anxiolytics/hypnotics. Patients using concomitant medications had an increased incidence of sexually related side effects and extrapyramidal side effects (EPS) at 6 months follow-up compared with patients not using concomitant medications. The results should be interpreted conservatively due to the observational design of SOHO.

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1. Introduction

Antipsychotic medications are the principal pharmacological treatment for patients with schizophrenia, but other psychotropic drugs are also commonly used to treat this disorder. Despite the high frequency of concomitant medication use in daily psychiatric practice (Parepally et al., 2002; Sacristan et al., 2000), the rationale for this is unclear and based on few studies.

The most frequently prescribed concomitant medications in schizophrenia are anticholinergics, benzodiazepines,
antidepressants, lithium and anticonvulsants. Anticholinergics are frequently prescribed for the treatment of extrapyramidal side effects (EPS). When used as concomitant medication, however, anticholinergics may worsen positive symptoms and decrease negative symptoms (Tandon and Dequardo, 1995), and are associated with impaired cognitive functioning of schizophrenic patients (Kasper and Resinger, 2003). Concomitant anticholinergic medication has also been assessed as a treatment for akathisia (Marsalek, 2000), and its effect on tardive dyskinesia is debatable (Soares and McGrath, 1997).

Investigations of benzodiazepines as adjunctive agents to conventional antipsychotic drugs have shown that they can reduce anxiety, insomnia, agitation, global impairment and psychotic symptoms (Stimmel, 1996; Wolkowitz and Pickar, 1991). Benzodiazepines are commonly used to treat neuroleptic-induced akathisia (Lima et al., 1999). The role of concomitant antidepreessant treatment in schizophrenia is uncertain, but a recent Cochrane systematic review concluded that there was no convincing evidence to support or refute the use of antidepressants for the treatment of depression in people with schizophrenia (Whitehead et al., 2002).

Antiepileptic drugs are also used as concomitant medications in schizophrenia. Based on evidence from randomised clinical trials, the anticonvulsant carbamazepine cannot be recommended for routine use in the treatment or augmentation of antipsychotic therapy for schizophrenia (Leucht et al., 2002). A recent clinical trial showed faster clinical improvement in psychopathology when divalproex was added to risperidone or olanzapine than with either antipsychotic alone (Casey et al., 2003).

Not only is there a lack of evidence for the clinical effectiveness of concomitant psychiatric medications, but also clinicians must consider the safety and tolerability of concomitant medications when prescribing them. Polypharmacy is an important risk factor for clinically relevant adverse drug reactions (Fattinger et al., 2000; Beyth and Shorr, 1999).

The results presented in this paper are from the European Schizophrenia Outpatient Health Outcomes (SOHO) study, an ongoing 3-year prospective, observational study of the treatment of schizophrenia in the outpatient setting in Europe (Haro et al., 2003a, 2005; Lambert et al., 2005). The aims of the present analyses were to evaluate the frequency of concomitant medication use in schizophrenia, examine how it varies with the type of antipsychotic drug the patient is receiving, determine factors associated with concomitant medication use, and describe how the use of concomitant medication impacts on treatment tolerability.

2. Methods

The SOHO study is being conducted in 10 European countries (Denmark, France, Germany, Greece, Ireland, Italy, The Netherlands, Portugal, Spain and UK) (Haro et al., 2003b). Local ethics committee approval was obtained in each country and all patients gave at least informed oral consent to participate in the study. Details of the study rationale, methods and recruitment have been published previously (Haro et al., 2003a).

2.1. Patient population

Participating psychiatrists were asked to include adult patients (≥18 years) who had initiated or changed antipsychotic therapy for the treatment of schizophrenia in an outpatient, ambulatory or community setting, irrespective of the reason for the change. All patient care was at the discretion of the participating psychiatrist; no instructions or recommendations for the provision of care or pharmacotherapy (medication doses, medications changes, use of concomitant medication) were included in the study protocol.

The main objective of the SOHO study is to evaluate the cost effectiveness of treatment with olanzapine compared with other antipsychotic medications in the treatment of patients with schizophrenia in the outpatient setting. The study includes patients taking any antipsychotic drug, but has a specific focus on the atypical antipsychotic olanzapine. In order to obtain more precise estimates of treatment outcomes with olanzapine, oversampling of this cohort was included in the study design. Therefore, the study was designed to provide two, approximately equal-sized, patient cohorts: (1) patients who initiated therapy with or changed to olanzapine; and (2) patients who initiated therapy with or changed to a non-olanzapine antipsychotic.

Participating psychiatrists were instructed to make treatment decisions before (and independently from) assessing each patient for enrolment. Different sample fractions entered each cohort to achieve approximately equal numbers in the two groups, leading to a stratified sample and oversampling of the olanzapine cohort.

2.2. Assessment of outcomes

Data were collected by psychiatrists during the normal course of treatment at the baseline assessment and at approximately 3- and 6-month follow-up. The following data were recorded: patient demographics, clinical course of schizophrenia, treatment, reason for treatment change, clinical severity, quality of life and social functioning. Clinical severity was assessed using a scale based on the Clinical Global Impression (CGI), 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., 2003c), 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 6 (among the
most severely ill patients). Quality of life was assessed using
the patient self-rated EuroQol questionnaire, and social
functioning was assessed using single-item questions.
Information about concomitant medication use was obtained
by recording whether or not patients received the following
concomitant medications: anticholinergics, antidepressants,
anxiolytics/hypnotics, and mood stabilizers. Medication
tolerability assessments included: weight, body mass index
(BMI), EPS, hyperprolactinaemia-related side effects (gynec-
comastia, galactorrhea, amenorrhea) and sexual dysfunction.

2.3. Statistical analysis

These analyses have been conducted including patients
who were prescribed only one antipsychotic (antipsychotic
monotherapy) after the baseline visit. The inclusion of
patients taking more than one antipsychotic would limit the
validity of the results, since the use of a second anti-
psychotic would be a confounding factor in the analysis.
Data were analyzed by treatment cohorts, which were
defined according to the antipsychotic initiated at the
baseline visit, irrespective of whether patients were still
receiving that medication after 6 months. Only those
treatment cohorts with at least 100 patients initiating
that antipsychotic at baseline were included in the analysis, and
were as follows: olanzapine, risperidone, quetiapine, amisul-
pride, clozapine, oral typical antipsychotic, and depot
typical antipsychotic. A subgroup analysis was conducted
using those patients who maintained the baseline antipsy-
chotic monotherapy throughout the 6-month follow-up.

No hypothesis testing in the univariate analysis was
conducted as this is an observational study. Multivariate
analysis was used to compare treatment cohorts because it
allowed adjustment for any differences between treatment
cohorts in the baseline covariates collected.

In the multivariate models, receiving treatment with a
concomitant medication was the dependent variable. A
generalised estimating equation (GEE) model with a logit
link and a repeated measurements approach was used. The
GEE models included three observations for each patient:
medication prescribed after the baseline visit, after the 3-
month visit, and after the 6-month visit. The autoregressive-
1 correlation matrix was used in this analysis because we
assumed that concomitant medication use was dependent on
the concomitant medication used at the previous visit.
Pairwise comparisons of each of the cohorts with the
olanzapine cohort are reported. Odds ratios (ORs) and 95%'
confidence intervals (95% CIs) are given for each of these
comparisons.

The following baseline covariates were used in the
models: concomitant medication use upon presentation at
the baseline visit (a variable for each of the concomitant
medications, i.e. anticholinergics, benzodiazepines, antide-
pressants, and mood stabilizers); antipsychotic initiated at
baseline (cohort); EPS; tardive dyskinesia; BMI; loss of
libido; amenorrhea; gynecomastia; galactorrhea; impotence/
sexual dysfunction; hostility; country; age; gender; age at
first treatment contact for schizophrenia; type of treatment
received in the 6 months prior to baseline assessment
(dichotomous variables for typical antipsychotic, depot
typical, clozapine, olanzapine, risperidone, other atypical);
receiving an antipsychotic upon presentation; reason for
change of medication (four dichotomous variables for
effectiveness, intolerability, compliance and patients
request); CGI-schizophrenia symptoms score (positive,
negative, depressive, cognitive, overall); compliance; cur-
rent substance dependency; current alcohol dependency;
visit; never treated with antipsychotics. Backward elimi-
nation was used for model reduction.

To analyze if there were differences in concomitant
medication use depending on antipsychotic drug dose, we
fitted each of the final concomitant medications models but
included new covariates that represented dose ranges (in
mg) for each atypical antipsychotic (<10, 10, and >10 mg
for olanzapine; <3, 3 to 6, and >6 mg for risperidone; <200,
200 to 400, and >400 for quetiapine and amisulpride; and
<100, 100 to 300 and >300 for clozapine). The dose ranges
were based on the antipsychotic doses prescribed in the
study.

A logistic regression model was fitted with the 6-month
data to analyze the frequency of side effects depending on
whether or not concomitant medication was used. Each
group of side effects (EPS, sexually related side effects and
weight gain) was the dependent variable in each model. The
covariates were the same as in the GEE models, except a
dichotomous variable indicating that the use of concomitant
medication was included and, obviously, the presence of
side effects was excluded from the covariates. Stepwise
elimination was used for model reduction.

3. Results

A total of 10 972 patients were enrolled in the SOHO
study. Of these, 8057 patients received as monotherapy at
the baseline visit, olanzapine (n = 4428), risperidone
(n = 1617), quetiapine (n = 610), amisulpride (n = 267),
clozapine (n = 276), oral typical antipsychotics (n = 490),
or depot typical antipsychotics (n = 369), and are included in
the analyses. The remaining 2915 patients were excluded
from the analysis due to failure to meet the entry criteria or
failure of cohort allocation (n = 766), because they were in
treatment cohorts with less than 100 patients (n = 24), or
because they received more than one antipsychotic at the
baseline visit (n = 2125). The baseline demographic and
treatment characteristics of the patients are summarised by
treatment cohort in Table 1. There were no major differences
between the treatment cohorts at baseline, except for the
clozapine cohort, which had a higher mean CGI-overall
score (3.78) than the other treatment cohorts (range 3.31 to
3.39). The proportion of patients using concomitant
medications at the baseline visit ranged from 53.2% to
66.3% across the cohorts. Anxiolytics/hypnotics were the most commonly used concomitant medications (by 28.5% to 46.7% of patients), followed by anticholinergics (18.4% to 29.4%) and antidepressants (9.5% to 25.1%).

At 6 months, data were available for a high proportion of patients in each treatment cohort (range 86.9% to 93.0%), and the majority of patients were still on the antipsychotic initiated at baseline (range 74.6% to 88.6%) (Table 2). A high proportion of patients in the clozapine, olanzapine and risperidone cohorts were still taking the antipsychotic started at baseline with no addition of other antipsychotics at the 6-month visit (83.9%, 83.1% and 78.3%, respectively) (Table 2, row 6). The mean and median doses of the various antipsychotics at baseline and at 6 months are given in Table 2.

Table 1 summarises the frequency of concomitant medication use at 3 and 6 months by antipsychotic cohort.

### Table 1
Baseline demographic and treatment characteristics by antipsychotic treatment initiated at baseline

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine</th>
<th>Risperidone</th>
<th>Quetiapine</th>
<th>Amisulpride</th>
<th>Clozapine</th>
<th>Oral typical</th>
<th>Depot typical</th>
</tr>
</thead>
<tbody>
<tr>
<td>N at baseline</td>
<td>4428</td>
<td>1617</td>
<td>610</td>
<td>267</td>
<td>276</td>
<td>490</td>
<td>369</td>
</tr>
<tr>
<td>Gender, %female</td>
<td>42.4</td>
<td>42.0</td>
<td>48.7</td>
<td>45.5</td>
<td>36.5</td>
<td>52.1</td>
<td>43.2</td>
</tr>
<tr>
<td>Age, years (mean±S.D.)</td>
<td>39.7±13.7</td>
<td>39.7±13.4</td>
<td>40.4±13.1</td>
<td>38.9±13.1</td>
<td>36.5±10.5</td>
<td>41.2±13.0</td>
<td>41.9±12.1</td>
</tr>
<tr>
<td>Never treated with antipsychotics, %</td>
<td>14.8</td>
<td>13.9</td>
<td>5.1</td>
<td>10.9</td>
<td>1.8</td>
<td>9.2</td>
<td>5.7</td>
</tr>
<tr>
<td>Received in the last 6 months, %patients</td>
<td>Typical antipsychotics</td>
<td>54.1</td>
<td>61.8</td>
<td>50.5</td>
<td>55.9</td>
<td>63.6</td>
<td>54.7</td>
</tr>
<tr>
<td></td>
<td>Clozapine</td>
<td>3.2</td>
<td>1.8</td>
<td>7.9</td>
<td>3.0</td>
<td>8.4</td>
<td>2.3</td>
</tr>
<tr>
<td></td>
<td>Olanzapine</td>
<td>5.2</td>
<td>11.0</td>
<td>23.3</td>
<td>16.2</td>
<td>16.0</td>
<td>13.3</td>
</tr>
<tr>
<td></td>
<td>Risperidone</td>
<td>21.5</td>
<td>6.5</td>
<td>24.5</td>
<td>19.6</td>
<td>27.6</td>
<td>19.1</td>
</tr>
<tr>
<td></td>
<td>Other atypical antipsychotics</td>
<td>8.5</td>
<td>6.9</td>
<td>9.0</td>
<td>12.8</td>
<td>9.1</td>
<td>9.2</td>
</tr>
<tr>
<td></td>
<td>None</td>
<td>21.8</td>
<td>22.2</td>
<td>8.9</td>
<td>16.5</td>
<td>4.0</td>
<td>19.2</td>
</tr>
<tr>
<td>Reason for change, %patients</td>
<td>Effectiveness</td>
<td>62.8</td>
<td>60.0</td>
<td>56.5</td>
<td>57.2</td>
<td>79.3</td>
<td>59.8</td>
</tr>
<tr>
<td></td>
<td>Intolerability</td>
<td>38.6</td>
<td>38.7</td>
<td>42.4</td>
<td>43.8</td>
<td>22.9</td>
<td>27.9</td>
</tr>
<tr>
<td></td>
<td>Compliance</td>
<td>14.0</td>
<td>12.3</td>
<td>12.9</td>
<td>16.0</td>
<td>11.5</td>
<td>13.5</td>
</tr>
<tr>
<td></td>
<td>Patient request</td>
<td>27.6</td>
<td>30.0</td>
<td>32.2</td>
<td>41.2</td>
<td>20.7</td>
<td>37.1</td>
</tr>
<tr>
<td>Concomitant medication use, %patients</td>
<td>Anticholinergic</td>
<td>21.3</td>
<td>27.8</td>
<td>19.0</td>
<td>18.4</td>
<td>29.4</td>
<td>23.5</td>
</tr>
<tr>
<td></td>
<td>Antidepressant</td>
<td>20.4</td>
<td>19.0</td>
<td>23.4</td>
<td>25.1</td>
<td>12.0</td>
<td>17.6</td>
</tr>
<tr>
<td></td>
<td>Anxiolytic/hypnotic</td>
<td>35.0</td>
<td>37.5</td>
<td>34.9</td>
<td>28.5</td>
<td>46.7</td>
<td>36.1</td>
</tr>
<tr>
<td></td>
<td>Mood stabilizer</td>
<td>8.2</td>
<td>6.6</td>
<td>11.6</td>
<td>4.9</td>
<td>14.5</td>
<td>9.6</td>
</tr>
<tr>
<td></td>
<td>Any concomitant use</td>
<td>57.2</td>
<td>60.1</td>
<td>61.2</td>
<td>53.2</td>
<td>66.3</td>
<td>58.4</td>
</tr>
<tr>
<td>CGI—Overall score, mean±S.D.</td>
<td>3.39±1.00</td>
<td>3.35±0.97</td>
<td>3.35±1.01</td>
<td>3.31±0.98</td>
<td>3.78±1.03</td>
<td>3.32±1.10</td>
<td>3.39±1.01</td>
</tr>
<tr>
<td>Extrapyramidal side effects, %</td>
<td>35.9</td>
<td>35.4</td>
<td>34.9</td>
<td>34.3</td>
<td>39.1</td>
<td>29.1</td>
<td>37.4</td>
</tr>
<tr>
<td>Tardive dyskinesia, %</td>
<td>8.7</td>
<td>7.6</td>
<td>10.9</td>
<td>12.2</td>
<td>11.0</td>
<td>8.6</td>
<td>8.8</td>
</tr>
<tr>
<td>Loss of libido, %</td>
<td>50.4</td>
<td>48.9</td>
<td>51.7</td>
<td>53.0</td>
<td>55.3</td>
<td>51.1</td>
<td>48.9</td>
</tr>
<tr>
<td>Amenorrhea, %</td>
<td>29.1</td>
<td>32.8</td>
<td>40.0</td>
<td>32.7</td>
<td>36.1</td>
<td>27.0</td>
<td>27.3</td>
</tr>
<tr>
<td>Impotence/sexual dysfunction, %</td>
<td>37.2</td>
<td>38.8</td>
<td>40.3</td>
<td>40.4</td>
<td>41.8</td>
<td>38.5</td>
<td>34.6</td>
</tr>
</tbody>
</table>

CGI Range: normal (0) to among the most severely ill (6). S.D., standard deviation.

Table 2 summarises the frequency of concomitant medication use at 3 and 6 months by antipsychotic cohort.

### Table 2
Treatment patterns by antipsychotic treatment initiated at baseline

<table>
<thead>
<tr>
<th></th>
<th>Olanzapine</th>
<th>Risperidone</th>
<th>Quetiapine</th>
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<td>610</td>
<td>267</td>
<td>276</td>
<td>490</td>
<td>369</td>
</tr>
<tr>
<td>N at 6 months</td>
<td>3924</td>
<td>1454</td>
<td>533</td>
<td>232</td>
<td>255</td>
<td>447</td>
<td>343</td>
</tr>
<tr>
<td>% with 6-month data</td>
<td>88.6</td>
<td>88.6</td>
<td>88.6</td>
<td>88.6</td>
<td>88.6</td>
<td>88.6</td>
<td>88.6</td>
</tr>
<tr>
<td>Still on drug initiated at baseline at 6 months⁵, %</td>
<td>88.6</td>
<td>84.3</td>
<td>74.9</td>
<td>74.6</td>
<td>88.2</td>
<td>79.9</td>
<td>84.3</td>
</tr>
<tr>
<td>Antipsychotic monotherapy at baseline, %</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Antipsychotic monotherapy at 6-month visit, %</td>
<td>83.1</td>
<td>78.3</td>
<td>64.4</td>
<td>68.1</td>
<td>83.9</td>
<td>75.8</td>
<td>74.1</td>
</tr>
<tr>
<td>Mean (±S.D.) dose at baseline, mg</td>
<td>10.7 (5.2)</td>
<td>4.4 (2.5)</td>
<td>252 (170)</td>
<td>358 (244)</td>
<td>155 (125)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Median dose at baseline, mg</td>
<td>10</td>
<td>4</td>
<td>200</td>
<td>400</td>
<td>100</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Mean (±S.D.) dose at 6 months, mg</td>
<td>11.8 (5.7)</td>
<td>4.9 (2.7)</td>
<td>375 (201)</td>
<td>397 (255)</td>
<td>235 (134)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Median dose at 6 months, mg</td>
<td>10</td>
<td>4</td>
<td>400</td>
<td>400</td>
<td>200</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

S.D., standard deviation.

Mean and median doses of oral and depot typical antipsychotics are not given because over 100 different preparations were used and chlorpromazine equivalents have not been calculated.

⁵ Patients may have had another antipsychotic added.
Some antipsychotics were associated with a lower use of concomitant medication than others. Anticholinergic use at 6 months in the olanzapine cohort (5.7%) was significantly lower than in all other treatment cohorts (range 9.3% to 25.7%), except the clozapine cohort (6.6%). Antidepressant use at 6 months was similar in all treatment cohorts (Table 3). Anxiolytic/hypnotic use was decreased from the baseline visit in all treatment cohorts at the 3- and 6-month visits. Compared with the olanzapine cohort (27.1%), anxiolytic use at 6 months was significantly greater in the risperidone (34.7%, OR 1.31; 95% CI 1.14, 1.49; \(P<0.0001\)), quetiapine (32.7%, OR 1.30; 95% CI 1.08, 1.56; \(P<0.01\)), and oral typical antipsychotic (34.1%, OR 1.51; 95% CI 1.23, 1.86; \(P<0.001\)) cohorts. There was little or no change from baseline in the percentage of patients using mood stabilizers at 6 months and the frequencies were similar in all cohorts.

The analysis of concomitant medication use according to antipsychotic medication dose gave similar results to the previous model. There was a dose-dependent relationship for risperidone with regards to anticholinergic use. When compared to olanzapine 10 mg, the odds ratios of using anticholinergics for risperidone <3 mg, 3 to 6 mg and >6 mg were 2.7 (95% CI 2.0, 3.4; \(P<0.0001\)), 3.2 (95% CI 2.5, 4.1; \(P<0.0001\)), and 6.0 (95% CI 4.2, 8.5; \(P<0.0001\)), respectively.

### 3.2. Subgroup analysis

Subgroup analysis of those patients who maintained the antipsychotic monotherapy prescribed at baseline throughout the 6-month follow-up period is summarised in Table 4. The results are similar to those in Table 3, except that the differences in anticholinergic use and anxiolytic/hypnotic use between the quetiapine and olanzapine cohorts were no longer statistically significant.

### 3.3. Multivariate analysis

Multivariate analysis of potential predictors of concomitant medication use is summarised in Table 5. There was a strong association between the use of concomitant medication before inclusion in SOHO and concomitant medication use in the follow-up period (ORs range from 13.2 to 78.3). There were large differences in concomitant medication use among countries. Concomitant medication use in Germany/Denmark (reference category) was lower than in most other countries. Anticholinergic use was highest in Greece and UK/Ireland, antidepressant use was highest in UK/Ireland and France, anxiolytic use was highest in France, Portugal and Italy, and mood stabilizer use was highest in Italy. There was a tendency for greater use of anxiolytics with increasing age. Female gender was associated with greater use of anti-
depressants. The presence of depressive symptoms was associated with the use of antidepressants and mood stabilizers. Patients with less prominent positive and negative symptoms were more likely to be prescribed antidepressants. Hostility was associated with the use of anxiolytics and mood stabilizers. Patients who were on antipsychotic treatment before baseline tended to use less concomitant medications after the baseline visit. Patients for whom the reason for medication change at inclusion in SOHO was lack of effectiveness tended to use more concomitant medications. EPS before baseline was associated with greater use of anticholinergics and anxiolytics. The presence of loss of libido before baseline was associated with greater use of antidepressants and anxiolytics. More compliant patients tended to be prescribed less anticholinergics and more antidepressants. Finally, patients who were abusing substances used less anticholinergics.

3.4. Side effects

The proportions of patients with sexual side effects, weight gain and EPS are summarised by concomitant medication usage at 6-month follow-up in Table 6. In most treatment cohorts, patients using concomitant medication had higher levels of sexual side effects and EPS than those not using concomitant medication. A logistic model was fitted to estimate the size of the effect after adjusting for confounding factors. The odds ratio of having sexually related side effects for patients taking concomitant medication compared to those not taking it was 1.2 (95% CI 1.09, 1.37; P<0.001). The odds ratio of having EPS for patients taking concomitant medication compared to those not taking it was 1.37 (95% CI 1.13, 1.65; P<0.005). There was no significant relationship between the use of concomitant medication and weight gain. The percentage of weight gained across all treatment cohorts was more than 50%, except for the quetiapine cohort (49.2%).

4. Discussion

Using data from the SOHO study, we have examined concomitant medication use in outpatients with schizophrenia who were receiving various atypical and typical antipsychotic agents. Concomitant medications are widely used in the treatment of patients with schizophrenia (Williams et al., 1999), but their use remains a debatable issue. Concomitant medications may be used to control side effects (e.g. use of anticholinergics for EPS), to augment the antipsychotic effects of antipsychotic agents in poorly responsive patients, or to control specific
symptoms of schizophrenia, such as anxiety, insomnia or depression. However, there is little scientific evidence to support the clinical utility of concomitant medications and their use can be associated with side effects, including a worsening of psychotic symptoms (Singh and Kay, 1978). Furthermore, polypharmacy increases the risk of adverse drug reactions (Beyth and Shorr, 1999; Fattinger et al., 2000) and poorer patient compliance with therapy (Marder, 2003).

4.1. Concomitant medication use

Concomitant medication use in our study was high, ranging from 5% to 29% for anticholinergics, 8% to 23% for antidepressants, 1% to 11% for anxiolytics, and 3% to 17% for mood stabilizers.
adverse effects, 22% to 37% for anxiolytics and 7% to 19% for mood stabilizers, depending on the type of antipsychotic prescribed. Our results suggest that the use of certain antipsychotics may be associated with less use of concomitant medication. In particular, olanzapine was associated with significantly less use of anticholinergics than risperidone, amisulpride and typical antipsychotics, and with less use of anxiolytics compared with risperidone and typical antipsychotics. The difference in use of anticholinergics and anxiolytics between the cohorts that started olanzapine and quetiapine at baseline was not considered to be clinically relevant because the subgroup analysis of those patients who maintained the antipsychotic monotherapy prescribed at baseline throughout the 6-month follow-up period showed that there was no significant difference in the use of anticholinergics and anxiolytic/hypnotic medications between the quetiapine and olanzapine cohorts. Since patients starting quetiapine had the highest rate of medication change, the finding of greater use of anticholinergics and anxiolytics in the quetiapine cohort could be related to those patients taking quetiapine who changed treatment and, thus, were taking other antipsychotics at the 6-month follow-up.

This is consistent with the previous studies, which reported that olanzapine-treated patients used fewer anticholinergics than those taking other antipsychotics (Parepally et al., 2002; Sacristan et al., 2000). In a recent study, Menzin et al. (2003) found that atypical antipsychotics were associated with significantly less use of concomitant anticholinergics and anxiolytics than conventional antipsychotics. Our findings support and extend these observations by demonstrating significant differences in concomitant medication use among atypical antipsychotics: e.g. patients receiving risperidone were more likely to use concomitant anticholinergics and concomitant anxiolytics than patients receiving olanzapine. The higher use of anxiolytics in the risperidone group is likely to be related to the higher rates of EPS experienced by risperidone treated patients (23.7% vs. 10.1% in the olanzapine group) as reported by Lambert and colleagues in the 6 months tolerability results of the SOHO study (Lambert et al., 2005).

Sacristan et al. (2000) also demonstrated a difference in the frequency of anticholinergic use after 6 months between olanzapine (10.2%) and risperidone (19.9%) groups. The less frequent use of anticholinergics in the olanzapine cohort at 6 months is consistent with the lower incidence of EPS in this group (Bobes et al., 2003).

4.2. Predictors of concomitant medication use

Our results show that antidepressants and mood stabilizers are used by patients with more severe depressive symptoms, and that anticholinergics and anxiolytics are used in patients with EPS. Higher intensity of positive symptoms was associated with lower use of antidepressants. This may relate to the fear that antidepressants could exacerbate psychotic symptoms (Plasky, 1991; Voon and Lang, 2004). Surprisingly, a higher intensity of negative symptoms was associated with lower use of antidepressants. This may be due to the fact that both negative and depressive symptoms were included in the statistical model and there was some correlation between the two variables. Upon removing depressive symptoms from the multivariate model, higher intensity of negative symptoms was associated with higher antidepressant use, which is consistent with other authors (Silver, 2004). As expected, patients who exhibited hostile behaviours received more anxiolytics and mood stabilizers. Likely this is due to the use of antiepileptics to treat more aggressive patients. Our results are in agreement with Hosak and Libiger’s (2002) review on the use of carbamazepine and valproate in patients who displayed a more hostile behaviour. In addition, we found that older patients use more anxiolytics, and that patients with a later age of onset of schizophrenia use less mood stabilizers and anxiolytics. Concomitant medication use was associated with a higher probability of side effects, particularly sexually related side effects (e.g. impotence, sexual dysfunction) and EPS.

Females in our study used more concomitant medication than males, especially antidepressants. This is consistent with the higher frequency of affective and anxiety symptoms in women. Females with schizophrenia are also more prone to side effects (Halbreich and Kahn, 2003; Leung and

### Table 6

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<th>Olanzapine</th>
<th>Risperidone</th>
<th>Quetiapine</th>
<th>Amisulpride</th>
<th>Clozapine</th>
<th>Oral typical</th>
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<th>Total</th>
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<td>Sexual side effects</td>
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*Patients taking anticholinergics were excluded from this analysis.*
Chue, 2000), which may increase in frequency with increased concomitant medication use, leading to a decrease in tolerability of antipsychotics.

A striking finding of the study was the large variation in concomitant medication use among the countries participating in SOHO (Denmark, France, Germany, Greece, Ireland, Italy, The Netherlands, Portugal, Spain and UK), even after adjusting for the type of antipsychotic drug used and patients’ clinical characteristics. This finding is in accordance with previous reports of antipsychotic treatment differences among countries (Haro et al., 2003b), and needs further exploration, but is beyond the scope of this paper.

4.3. Side effects

There was substantial weight gain after 6 months of treatment in all treatment cohorts. The percentage of weight gained across all cohorts was more than 50%, except for the quetiapine cohort (49.2%). Weight gain was highest for the olanzapine cohort. Detailed analysis and discussion of weight changes during the first 6 months of the SOHO study have been published elsewhere (Lambert et al., 2005) and, therefore, will not be discussed further in this paper.

4.4. Methodological issues

Since SOHO is an observational study, some patients included in the study were receiving more than one antipsychotic. In order to study how each antipsychotic drug impacts on concomitant medication use, we restricted our analyses to those patients prescribed only one antipsychotic medication at the baseline visit. The analyses were conducted regardless of the maintenance of that antipsychotic during the 6 months follow-up. To determine whether antipsychotic treatment changes affected the results, we performed a subgroup analysis on those patients who remained on the same monotherapy throughout the 6-month follow-up period. By restricting the analysis to include only those patients receiving one antipsychotic, we may have biased our sample by excluding more severe cases (i.e. patients for whom the treating psychiatrist prescribed more than one antipsychotic) and, thus, may have caused an underestimation of actual concomitant medication usage in usual clinical practice. This may be clinically relevant because prescription of combination treatment with more than one antipsychotic is common practice among some psychiatrists.

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, it may imply some limitations. First, the sample of patients included in SOHO is not directly representative of the population of patients starting a new antipsychotic in the outpatient setting. However, this limitation may not be relevant when we study the longitudinal effects on patients who start each medication. Second, the effect of having a large sample of olanzapine patients is that we are able 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. For this reason, our analyses have focused solely on the comparison of olanzapine vs. other antipsychotics. Finally, the oversampling technique could introduce recruitment bias. The study protocol asked participating psychiatrists to make decisions about changing a patient’s medication and the type of antipsychotic prescribed before, and independently of, any decision to include that patient in the study. However, as the choice of antipsychotic is often based on the clinical impression of the psychiatrist, there may have been some cases where the psychiatrist had not decided which specific antipsychotic to prescribe, and their decision to prescribe olanzapine was influenced by the existence of the SOHO study.

A further limitation of the study is that assignment to treatment cohort was not random: psychiatrists decided which drug to initiate in which patients and at what dose. As a result, there could be relevant differences between the patients in each medication group, which were probably not directly comparable. To control for these cohort differences, we used multivariate analysis that adjusted for all observed baseline differences between cohorts. Previous research has found that when observational studies have appropriate designs and analysis strategies, comparisons of the findings of randomised controlled trials and observational studies reveal no major differences in the effects of treatments (Benson and Hartz, 2000).

The SOHO study has several strengths worth mentioning. First, because it is unprecedented in size, powerful statistical techniques can be used to control for confounding factors. Second, there was a very high retention rate in the study at 6 months (88.5%), much higher than that seen in randomised clinical trials, where high drop-out rates can limit the drawing of firm conclusions (Duggan et al., 2003).

5. Conclusions

This study has found that concomitant medication use is high and varies according to the specific antipsychotic used in outpatients with schizophrenia. Some atypical antipsychotics, such as olanzapine, clozapine and quetiapine, are associated with less use of concomitant medication. The advantages of reduced concomitant medication usage could include a reduction in potential drug interactions and a better tolerability profile. This could lead to improved patient compliance with treatment, which needs to be explored in future studies. The results should be interpreted conservatively due to the observational design of the study.
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