Observational study of outpatients with schizophrenia in the Middle East and Africa — 3- and 6-month efficacy and safety results

The Intercontinental Schizophrenia Outpatient Health Outcomes Study

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Objectives. To examine the comparative outcomes associated with the antipsychotic treatment of outpatients with schizophrenia and to describe changes in clinical status over the first 6 months of treatment in participating patients from the Middle East and Africa (MEA).

Methods. The Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) Study is a 3-year, prospective, observational study of health outcomes associated with antipsychotic medication in outpatients treated for schizophrenia. This article reports the 6-month interim results in the MEA region (N = 1399). Subjects, aged 18 years and over and undergoing treatment for schizophrenia were enrolled if, at the discretion of the treating psychiatrist, they initiated or changed antipsychotic medication. For the primary analyses, two treatment groups were established; viz. olanzapine and 'other antipsychotics' (non-olanzapine including risperidone) groups. Subanalysis of olanzapine versus risperidone groups was also done as secondary comparison. Measures of treatment effectiveness (Clinical Global Impression of Severity (CGI-S)), and safety (incidence of extrapyramidal symptoms (EPS), tardive dyskinesia (TD), side-effects (sexual dysfunction and weight change)) were taken at baseline and at 3 and 6 months after enrolment.

Results. Olanzapine (58.9%) and risperidone (13.8%)) were the most frequently prescribed antipsychotics in this study. Co-prescription of anticholinergics was at least four times more frequent for risperidone-treated patients than for those treated with olanzapine at any time point. Olanzapine was more efficacious in the treatment of overall symptom severity (CGI-S) than other antipsychotics or risperidone. In all other symptom domains (CGI-S), patients responded significantly better to treatment with olanzapine than to treatment with other antipsychotics. EPS significantly declined over the treatment period for patients taking olanzapine. Compared with patients on other antipsychotics, fewer patients receiving olanzapine therapy developed TD post-baseline. In addition, more patients on olanzapine therapy presented with a remission of TD symptoms after 3 and 6 months of treatment compared with patients on other antipsychotics and risperidone. The prevalence of side-effects associated with sexual function (loss of libido, impotence/sexual dysfunction) was significantly reduced ($p < 0.001$) with olanzapine treatment compared with other antipsychotics. Compared with those patients taking other antipsychotics or risperidone, fewer patients developed loss of libido, and more patients recovered from these symptoms in the course of 6 months of olanzapine treatment. Similarly, fewer olanzapine patients suffered from impotence/sexual dysfunction over the first 3 months of treatment, and more patients had recovered from pre-existing symptoms after 6 months than those taking other antipsychotics or risperidone. Patients taking olanzapine were significantly more likely to gain more than 7% of their baseline weight over a 6-month period.

Conclusions. Initial 3- and 6-month findings included in this progress report indicate that patients treated with olanzapine showed greater improvements in terms of effectiveness of treatment, and that this was associated with a more favourable overall safety profile than that of patients treated with other antipsychotics or risperidone.

Randomised clinical trials are considered standard experiments in comparing the safety and efficacy of antipsychotics in the treatment of schizophrenia. While more than 2 000 controlled research trials have been conducted into schizophrenia in the last 50 years, according to a review[1] these trials suffer from limitations in some areas: the follow-up period was less than 6 weeks in 54% of trials, 6-month follow-ups were found in only 19% of them, and mere 20 trials raised the issue of statistical power.[1] These trials were rarely community-based, they usually enrolled small numbers of patients and the exclusion and inclusion criteria and the setting design of these studies differed from everyday practices, such that the results reflect these experimental conditions and are not representative of all patients or all clinicians. There are also few data available from controlled trials that consider quality-of-life issues or clinically relevant functional outcomes. On the other hand, controlled clinical trials are very important to provide sufficient efficacy and safety data for regulatory agencies, and these trials are always the first step in providing data on whether a treatment works in clinical research settings.

However, if the effects of treatment in usual clinical practice lie within the scope of interest, prospective observational studies are useful to evaluate effectiveness. The value of observational studies is becoming more widely accepted.[2] Only relatively few naturalistic studies have been conducted comparing atypical antipsychotics in real-life circumstances. These studies also have limitations: their design is usually cross-sectional or retrospective, the samples are small, they are usually limited in terms of scope and lack a good comparison group, and there is no benefit from randomisation or blinding. Because of these differences, controlled trials and observational studies have complementary value for physicians.

Research articles have frequently reported the advantages of atypical antipsychotics over older, conventional neuroleptics, advantages such as the markedly reduced incidence of side-effects (extrapyramidal symptoms (EPS), tardive dyskinesia (TD) and seizures).[3,4] Randomised, controlled, clinical trials based on inpatients with schizophrenia provide evidence that treatment with olanzapine is associated with improvements in positive, negative, depressive, and cognitive symptoms, while also demonstrating safety profile differences and advantages.[5,6] In addition, these clinical trials also provide evidence that olanzapine is associated with reduced suicidality, reduced suicide-attempt rates, improved patient functioning, improved health-related quality of life, and equal or lower consumption of a range of health care resources.[7] Risperidone also provided the same evidence under controlled circumstances.[8,9]

Olanzapine and risperidone have also demonstrated superior efficacy and tolerability when compared with either placebo or conventional neuroleptics in controlled trials.[10] Carrasco *et al.*[11] have reported that olanzapine may be considered a first-line treatment for severely psychotic inpatients with schizophrenia. Although there are selected examples of studies that have evaluated experience with olanzapine outside of the clinical research setting,[2-16] there is a need for studies that have broadly evaluated clinical outcomes, tolerability and patient functioning. Thus, there are still some questions unanswered regarding the extent to which measurement of treatment outcomes in practice settings will be able to confirm the findings of clinical trials and the extent to which such outcomes may vary between different patient subgroups and social and medical cultures.

We report here on the 6-month interim results of the analyses performed for the ongoing Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study, a 3-year observational study of the treatment regimens of patients with schizophrenia in the Middle East and Africa (MEA) region. This large-scale study is being conducted to satisfy the need for additional information from diverse, real-practice settings regarding the clinical and health outcomes of antipsychotic medication therapy for schizophrenia patients.

Methods

Study design and patients

The main aim of the 6-month analysis was to explore trends within the patient population of this study using the analysis methods outlined in the predefined statistical analysis plan. IC-SOHO is a non-interventional, observational study. All patient care is at the discretion of the participating psychiatrists. The naturalistic care provided and the outcomes of that care for enrolled patients will be recorded for the duration of the study. Patients were enrolled using a non-randomised process, alternating between group 1 and group 2. Blocks of 10 patients were used, 5 for group 1 and 5 for group 2. Every psychiatrist was requested to enrol at least 1 block of 10 patients with 5 patients in each cohort. Those patients who received olanzapine were enrolled into group 1, and those who received other antipsychotics into group 2. As a result of this enrolment method, 50% of patients were assigned to the olanzapine group, and 50% to the other antipsychotic group. Investigators were instructed to make treatment decisions independent of the study and then to evaluate whether patients were eligible for inclusion based on entry criteria and the alternating

method of enrolment. Data collection will be conducted for a minimum of 36 months. This multicentre study aimed to enroll 7 648 patients from the regions of Latin America, Africa, the Middle East and Central and Eastern Europe. This progress report describes the 6-month interim efficacy and safety results in the Middle East and Africa region (*N* = 1 399) and complements the baseline IC-SOHO report.[17]

The intent-to-treat approach was used as the primary analysis method. This means that patients were analysed according to the group they originally entered regardless of which medication they took subsequently. The study enables a direct comparison of olanzapine versus other antipsychotic medications. To accomplish this goal, a multicentre study was implemented to allow for multiple, country-specific and area-specific analyses. Because the same data will be collected in each country, this allows for global analyses from the pooled data.

Participating psychiatrists were trained in the study procedures and at their discretion they offered entry to patients with a clinical diagnosis of schizophrenia (*International Classification of Diseases (ICD) 10* or *Diagnostic and Statistical Manual (DSM IV)*) who met the following criteria: (*i*) initiated or changed antipsychotic medication for the treatment of schizophrenia; (*ii*) presented with the normal course of care in an outpatient setting or in a hospital when admission was planned for the initiation or change of antipsychotic medication with discharge planned within 2 weeks; (*iii*) at least 18 years of age; and (*iv*) not simultaneously participating in an interventional study. Patients were required to provide at least verbal consent to enable release of their personal information; written consent requirements were determined by local regulations in each participating country. Data were obtained during visits that constituted the patients' normal course of treatment. The different ethics requirements for this type of study were met in each participating country.

Outcome measurements

For primary analyses, two major treatment groups were compared: olanzapine and 'other antipsychotics' (other meaning all antipsychotics, other than olanzapine, including risperidone). Subanalysis of the olanzapine versus risperidone groups was also done as secondary comparison. The comparison was based on the Clinical Global Impression - Severity (CGI-S) scores of depressive, negative, positive, cognitive and overall symptoms; dosage; side-effects, EPS, TD, sexual dysfunction; and body weight/body mass index (BMI).

Efficacy of treatment was explored through the assessment of the severity of symptoms with regard to positive, negative, depressive, cognitive and overall CGI symptom severity at each visit. Symptom severity variables were captured on a scale of 0 - 6 (transformed to a scale of 1 - 7 for this analysis), with 0 (1) being normal and 6 (7) being the most severely ill. Efficacy measures were analysed at each visit and for each of the treatment groupings outlined above. Clinical response was defined from baseline to the current visit as any improvement in CGI overall symptom severity of 2 points or more if the baseline severity was over 3 (4 on the new scale) or an improvement of 1 point or more if the baseline severity was less than or equal to 3 (4).

Patient baseline demographics, treatment patterns throughout the study, prescription of concomitant medications, and treatment tolerability as assessed by adverse events, questionnaires and weight measurements were also recorded.

Statistical analysis

The statistical analysis was conducted by an Eli Lilly and Company statistician at the Clinical Outcomes and Research Institute (CORI), Australia, following the predefined Statistical Analysis Plan written for this study for the 6-month analysis. Statistical calculations were carried out using SAS System for Windows (Release 8.02, SAS Institute Inc., Cary, NC, USA). Because multiple comparisons were tested, the cut-off level for significance for all analyses was determined, a priori, to be $p = 0.001$. Because of the subanalysis, non-significant *p*-values between 0.05 and 0.001 are also presented in this article.

Descriptive methods were used to analyse the parameters with statistical comparisons between treatment groups. The following statistical tests were used to calculate *p*-values when analyses were performed: the two-sample *t*-test was used as a statistical test comparing the mean of two groups. The chi-squared test was used to determine if there was any evidence of an association between two categorical variables. Fisher's exact test does the same, but calculates exact rather than asymptotic *p*-values. The Cochran Mantel-Haenszel mean score was used when one variable was ordinal and the other variable categorical. It compares the mean of the ordinal variable between each of the categories of the second variable to determine if there is any evidence of difference between each level of the categorical variable in terms of the ordinal variable. The Cochran Mantel-Haenszel correlation test determines if there is any evidence of association between two ordinal variables.

Results

Patient population

There were 1 399 patients enrolled in the AMEA region. The rate of enrolment by country was 49.5% in Turkey (*N* = 692), 21.9% in Algeria (*N* = 306), 14.6% in Saudi Arabia (*N* = 204), and 14.1% in Egypt (*N* = 197). The patient treatment groups have similar baseline demographic characteristics (Table I). The mean age in the olanzapine group (*N* = 616) was 32.5 years (standard deviation (SD) 10.2 years). The mean age in the 'other antipsychotics' group (*N* = 572) was 32.4 years (SD 10 years). (In the risperidone group (*N* = 154) it was 31.9 years (SD 10.6 years). The mean age difference between the three groups was not significant. The proportion of treatment-naïve patients in the olanzapine and the 'other antipsychotics' treatment group was 20% and 16%, respectively.

Prescription for antipsychotics at baseline

Olanzapine (58.9%) and risperidone (13.8%) were the most frequently prescribed antipsychotics in this study. The breakdown of all other antipsychotics at baseline was as follows: amisulpiride (1.0%), chlorpromazine (1.5%), clozapine (4.9%), flupentixol (1.8%), fluphenazine (0.3%), haloperidol (5.8%), levomepromazine (0.6%), olanzapine (58.9%), pimozide (1.1%), pipotiazine (0.3%), quetiapine (3.6%), risperidone (13.8%), sulpiride (1.5%), thioridazine (0.6%), trifluoperazine (0.8%), and zuclopenthixol (3.5%).

Dosage

The mean dose (±SD) for olanzapine at baseline, 3 months and 6 months was 12.2 ± 4.5 mg, 13.2 ± 5.1mg and 13.2 ± 5.1mg, respectively. The modal dose for olanzapine was 10 mg at all of the visits (baseline, 3 months and 6 months). The mean dose (± SD) for risperidone at baseline, 3 months and 6 months was 4.4 ± 1.9, 4.9 ± 2.4 and 4.9 ± 2.5 mg, respectively. The modal dose for risperidone was 4 mg at baseline and 6 mg at 3 months and 6 months.

Efficacy analysis

The results of the change in overall CGI-S score and the other CGI-S scores from baseline to 3 and 6 months for patients on olanzapine, other antipsychotics or risperidone are shown in Table II. Patients taking olanzapine showed significantly greater improvement in overall symptom severity following 3 and 6 months of treatment, than patients taking other antipsychotics or risperidone ($p < 0.0001$ for olanzapine v. 'other' at 3 and 6 months, and olanzapine v. risperidone after 3 and 6 months, *t*-test). With regard to the results of the change in positive, negative, depressive and cognitive CGI scores from baseline to 3 and 6 months for patients on olanzapine, other antipsychotics or risperidone, patients taking olanzapine showed significantly greater improvement in positive symptom severity following 3 and 6 months of treatment, compared with patients taking other antipsychotics ($p < 0.0001$ for olanzapine vs. 'other' at 3 and 6 months).

The results of the change in positive, negative, depressive and cognitive CGI scores comparing the olanzapine group with the risperidone group were not significant ($p < 0.05$ for olanzapine v. risperidone at 3 and 6 months, *t*-test).

Safety

Extrapyramidal side-effects and tardive dyskinesia

Safety was assessed by examining the changes in dystonia/akathisia/parkinsonism (EPS) and TD from baseline to 3 months and 6 months. Safety data were explored for all patients. These analyses were performed across the treatment groups defined above.

The proportion of patients with EPS and TD on olanzapine, risperidone or other antipsychotics at 3 and 6 months is shown in Table III. There was no significant difference in the prevalence of EPS at baseline in different treatment groups. The proportion of patients with EPS declined significantly in patients taking olanzapine compared with patients taking other antipsychotics or risperidone at 3-

Table I. Patient characteristics at baseline

Patient characteristic	Olanzapine	'Other antipsychotics'*	Risperidone
Number of patients	616	572	154
% Male	64	67	56
% Female	36	33	44
Mean age (SD)	33 (10)	32 (10)	32 (11)
% Neuroleptic-naïve	20[9]	16[†]	18

* Other = all antipsychotics, other than olanzapine, including risperidone.
†$p = 0.0423$ olanzapine v. 'other antipsychotics', chi-squared test.

Table II. Change in CGI score symptom domains from baseline to 3 and 6 months for patients on olanzapine, 'other antipsychotics' and risperidone

CGI symptom domains	Treatment	Clinical Global Impressions (CGI) 1 - 7 score (mean (SD)) Baseline	3 months	6 months
Overall	Olanzapine	4.6 (1.0)	3.2 (1.1)	2.7 (1.1)
	Other	4.6 (1.0)	3.7 (1.1)*	3.4 (1.2)*
	Risperidone	4.6 (1.1)	3.6 (1.1)†	3.2 (1.1)‡
Positive	Olanzapine	4.4 (1.4)	2.9 (1.3)	2.4 (1.3)
	Other	4.5 (1.4)	3.4 (1.3)*	3.0 (1.3)*
	Risperidone	4.4 (1.4)	3.4 (1.2)‡	2.9 (1.3)‡
Negative	Olanzapine	4.1 (1.4)	3.0 (1.2)	2.5 (1.2)
	Other	4.1 (1.3)	3.4 (1.2)*	3.2 (1.2)*
	Risperidone	4.1 (1.3)	3.4 (1.1)‡	3.0 (1.1)‡
Depressive	Olanzapine	3.3 (1.5)	2.4 (1.2)	2.1 (1.1)
	Other	3.3 (1.4)	2.8 (1.3)*	2.5 (1.2)*
	Risperidone	3.6 (1.3)	3.0 (1.3)‡	2.6 (1.3)
Cognitive	Olanzapine	3.8 (1.4)	2.7 (1.2)	2.3 (1.1)
	Other	3.8 (1.3)	3.2 (1.3)*	3.0 (1.2)*
	Risperidone	4.0 (1.2)	3.3 (1.2)‡	2.9 (1.2)‡

*$p < 0.0001$, olanzapine v. 'other antipsychotics' at 3 and 6 months, t-test (comparison in mean change).
†$p < 0.0001$, olanzapine v. risperidone at 3 and 6 months, t-test (comparison in mean change).
‡$p < 0.05$, olanzapine v. risperidone at 3 and 6 months, t-test (comparison in mean change).

and 6-month visits ($p < 0.0001$). Compared with patients taking risperidone or other antipsychotics, significantly fewer patients on olanzapine developed EPS ($p < 0.0001$, chi-squared test, Table IV). Also, more olanzapine patients exhibited a remission of EPS. Co-prescription of anticholinergics was at least four times more frequent for risperidone-treated patients than for those treated with olanzapine (for olanzapine-treated patients at baseline, 3 months and 6 months: 9%, 4% and 3% respectively; for risperidone-treated patients: 42%, 50% and 45% respectively).

The proportion of patients with TD declined over the first 3 months of treatment, and remained stable at 6 months in the olanzapine and risperidone groups. This decline in TD was most pronounced in patients taking olanzapine. Fewer patients developed TD following 3 and 6 months of olanzapine treatment when compared with patients taking other antipsychotics ($p < 0.05$; chi-squared test).

Sexual dysfunction

Olanzapine treatment was associated with a decline in the incidence of loss of libido at 3 and 6 months (Table V.) Fewer patients

Table III. Proportion of patients with extrapyramidal side-effects (EPS) and tardive dyskinesia (TD) taking olanzapine, 'other antipsychotics' or risperidone at baseline, 3 and 6 months

		Baseline	3 months	6 months
EPS (% of patients)	Olanzapine	36.0	8.7	5.5
	'Other antipsychotics'	39.4	39.4*	36.9*
	Risperidone	36.3	37.6*	34.3*
TD (% of patients)	Olanzapine	5.5	1.5	1.2
	'Other antipsychotics'	7.2	9.4*	5.9*
	Risperidone	5.7	3.4*	3.6*

*$p < 0.0001$ chi-squared test, olanzapine v. risperidone or olanzapine v. 'other antipsychotics'.

Table IV. Proportion of patients with treatment-emergent EPS and TD and remission of EPS and TD when taking olanzapine, other antipsychotics or risperidone at 3 and 6 months

	Duration of treatment (months)					
	Olanzapine		Other		Risperidone	
	3	6	3	6	3	6
% of patients with treatment-emergent EPS	4*	3*	25*	25*	20*	17*
% of patients with remission† of EPS	83*	90*	40*	44*	35*	39*
% of patients with treatment-emergent TD	0.4‡	0.4‡	4.9‡	3.1‡	0.7	1.6
% of patients with remission† of TD	79‡	87‡	33‡	50‡	50	57

*$p < 0.0001$ chi-squared test, olanzapine v. risperidone or olanzapine vs. 'other antipsychotics'.
†Present at baseline, no longer present at 3 or 6 months.
‡$p < 0.05$ chi-squared test.
EPS = extrapyramidal side-effects; TD = tardive dyskinesia.

developed loss of libido, and more patients had a remission of symptoms following 3 and 6 months olanzapine treatment compared with patients taking other antipsychotics, including risperidone ($p < 0.05$, chi-squared test). The proportion of patients with impotence/sexual dysfunction was significantly lower after 3 and 6 months of treatment with olanzapine. Fewer patients developed impotence/sexual dysfunction following 3 and 6 months of olanzapine treatment compared with patients taking other antipsychotics, including risperidone ($p < 0.05$, chi-squared test, Table VI). More olanzapine patients experienced a remission of symptoms at 6 months than those taking other antipsychotics, including risperidone. Additionally, significantly fewer patients taking olanzapine suffered from menstrual disturbances compared with patients taking other antipsychotics at 3 and 6 months ($p < 0.001$, chi-squared test).

Weight changes

The change in patients' weight over time was analysed for all analyses, as was the indicator of whether weight had increased by more than 7% from baseline to 3 and 6 months. Patients on olanzapine therapy gained significantly more weight than those taking other antipsychotics (Table VII). The mean change in BMI of patients on olanzapine therapy was significantly greater than that of patients taking other antipsychotics. The proportion of patients who gained more than 7% of their baseline weight during the 6-month treatment period was significantly higher for olanzapine patients than for those on other antipsychotics. There was no significant difference between the olanzapine and the risperidone groups in mean BMI change and percentage of patients with > 7% increase in weight ($p > 0.05$).

Discussion

The ratio of males to females and the mean age of patients enrolled in the observational IC-SOHO study were consistent with prevalence-based samples of individuals with schizophrenia treated in outpatient facilities.[17]

Olanzapine was more efficacious in the treatment of overall symptom severity (CGI) than risperidone or other antipsychotics.

Table V. Proportion of patients with loss of libido and impotence/sexual dysfunction treated with olanzapine, risperidone or other antipsychotics

Incidence	Therapeutic group	Baseline	3 months	6 months
Loss of libido (% of patients)	Olanzapine	47.7	36.1	29.7
	Other antipsychotics	51.4	53.0*	48.4*
	Risperidone	46.5	50.4†	45.2‡
Impotence/sexual dysfunction (% of patients)	Olanzapine	42.0	25.0	22.8
	Other antipsychotics	45.7	43.4*	38.0*
	Risperidone	42.4	43.3*	35.7†

*$p < 0.0001$, chi-squared test.
†$p < 0.05$, chi-squared test.
‡$p < 0.001$, chi-squared test.

Table VI. Proportion of patients with treatment-emergent loss of libido and impotence/sexual dysfunction and remission of these symptoms when treated with olanzapine, other antipsychotics or risperidone at 3 and 6 months

	Duration of treatment (months)					
	Olanzapine		Other		Risperidone	
	3	6	3	6	3	6
% of patients with treatment-emergent loss of libido	11*	13*	21*	23*	21*	18
% of patients with remission† of loss of libido	35*	50*	17*	29*	16*	24*
% of patients with treatment-emergent symptoms of impotence/sexual dysfunction	6*	9*	15*	17*	15*	10
% of patients with remission† of symptoms of impotence/sexual dysfunction	48*	58*	22*	36*	20*	31*

*$p < 0.05$, chi-squared test.
†Present at baseline, no longer present at 3 or 6 months.

Table VII. Change in weight and BMI of patients on olanzapine, risperidone or other antipsychotic therapy at 6 months

	Olanzapine	Other	Risperidone
Mean weight change (kg) (± SD)	4.3 (5.1)	2.5 (4.7)*	3.0 (4.5)†
Mean BMI change (± SD)	1.4 (2.5)	0.9 (1.7)*	1.1 (1.6)
% of patients with > 7 % increase in weight	38	27‡	32

*$p \leq 0.0001$ olanzapine v. other , *t*-test.
†$p \leq 0.05$ olanzapine v. risperidone, *t*-test.
‡$p \leq 0.0001$ olanzapine v. other, chi-squared test.

In all other symptom domains (CGI), patients responded significantly better to treatment with olanzapine than to treatment with other antipsychotics. Our study adds to the findings of a recent study[18] which suggested that these atypical antipsychotics are not truly different in their efficacy or that differences in efficacy were obscured in the more complex setting of real-world practice. This difference may be owing to the fact that the patients in the study by Sernyak *et al.*[18] were older than the IC-SOHO population, and there was a relatively high number of newly diagnosed neuroleptic-naïve patients in the IC-SOHO study (16 - 20 %).

To our knowledge, the IC-SOHO study is the first large, long-term, prospective, multi-centre, naturalistic study comparing olanzapine, risperidone and other antipsychotics. In an international retrospective naturalistic study, Kasper *et al.*[14,19] investigated the efficacy, tolerability and health economic data from the Risperidone Olanzapine Drug Outcomes studies in Schizophrenia (RODOS) programme. The population included in the RODOS study consisted of 1 901 inpatients with diagnoses of schizophrenia or schizoaffective disorder. Comparing dosages in these studies, it will be noted that in our study the mean dose for olanzapine and risperidone was lower than in the RODOS study. (In the IC-SOHO study, the mean (± SD) dose for olanzapine was 12.2 (± 4.5), 13.2 (± 5.1) and 13.2 (± 5.1) mg at baseline, 3 and 6 months respectively, and the mean dose (± SD) for risperidone was 4.4 (± 1.9), 4.9 (± 2.4) and 4.9 (± 2.5) mg. In the RODOS study[19] the mean ± SD daily dose of olanzapine treatment was 14.5 ± 5.1 mg compared with 5.3 ± 2.6 mg for risperidone). This difference can be explained by the fact that the patients in the RODOS study[19] were more severe cases than in the IC-SOHO study, because they were inpatients. Olanzapine was found to be more efficacious than risperidone or other antipsychotics in the IC-SOHO study using a prospective design in the treatment of outpatients suffering from schizophrenia as measured by the overall CGI-S scores. Different scales were used to measure the results of the two studies — in the retrospective RODOS design the treatment was assessed as 'effective', 'partially effective' or 'not effective', and for the purposes of analysis, partially effective treatment was considered to be effective. Treatment was considered to be effective in significantly more patients in the risperidone group than in the olanzapine group (84% risperidone group, $N = 765$, versus 79% olanzapine group, $N = 766$, $p = 0.01$) in the RODOS study.

The efficacy results of the IC-SOHO 3- and 6-month data are in line with the outcome of the Estudio Farmacoepidemiologico en la Esquizofrenia con Olanzapina (EFESO) study.[12,13] The EFESO study, a 6-month prospective, observational, naturalistic study conducted in Spain, was designed to assess outcomes with olanzapine compared with other antipsychotic drugs in the treatment

of outpatients with schizophrenia (*N* = 2 967). Clinical improvement at endpoint at 6 months, measured by the mean change in the CGI-S and the Global Assessment of Functioning (GAF), was significantly higher in the olanzapine group compared with the control group of other antipsychotics in this study ($p = 0.004$).

The proportion of patients with EPS significantly declined over the treatment period for patients taking olanzapine at 3- and 6-month visits in our study. Compared with patients taking other antipsychotics or risperidone, significantly fewer patients on olanzapine developed EPS. This can be attributed to the significantly lower number of new cases and higher rates of remission seen in this patient population. This difference also reflected the greater need for anticholinergic medications in patients taking risperidone. These results are in contrast with the findings that the RODOS study[19] reported — they found that EPS occurred in 1.7% of risperidone patients and 2% of olanzapine patients. However, the EFESO study supports our findings — Sacristan *et al*.[13] reported that a significantly lower proportion of olanzapine-treated patients (36.9%) experienced EPS compared with risperidol-treated patients (49.6%), and a significantly lower proportion of olanzapine-treated patients (10.2%) were receiving concomitant anticholinergic medication at the end of the study (month 6) compared with risperidone-treated patients (19.9%). This favourable safety profile of olanzapine in terms of EPS has also been confirmed in a naturalistic study of inpatient schizophrenics.[20]

In the IC-SOHO study, more patients receiving olanzapine therapy presented with remission of TD symptoms, which can be explained by the beneficial effect of olanzapine on TD in patients with schizophrenia. This finding is in line with the results of the study by Kinon *et al*.[21]

Although it has long been recognised that typical antipsychotic drugs have been associated with symptomatic hyperprolactinaemia, which in turn can lead to a disruption of sexual function, spontaneous reporting of adverse events underestimates the incidence and prevalence of sexual dysfunction.[22,23] In the light of this fact, an important finding of our study is that the prevalence of side-effects associated with sexual function (loss of libido, impotence/sexual dysfunction and menstrual disturbances) was significantly reduced in patients receiving olanzapine treatment, compared with those treated with other antipsychotics. Our study also suggests that switching to olanzapine is a safe and effective alternative method for patients with antipsychotic-induced hyperprolactinaemia-associated sexual dysfunction.

More than half of the patients enrolled in the IC-SOHO study were already overweight (46%) or obese (8%).[17] In our study, patients taking olanzapine were significantly more likely to gain > 7% of their baseline weight over a 6-month period. The degree of weight gain associated with antipsychotic treatment in real-life practice may be less than that seen in the clinical trials.[24,25]

Because of the observational nature of this study, there are some limitations when interpreting the data. Observational studies have inherent limitations such as sample size differences between treatment groups. The patients in our study were outpatients, and therefore not reflective of severe cases. However, Carrasco *et al*.[11] also reported in a naturalistic study that olanzapine may be considered a first-line treatment for severely psychotic inpatients with schizophrenia. In the latter study, the mean change from baseline to endpoint of overall symptomatology (total Brief Psychiatric Rating Scale (BPRS) score) was significantly greater in the olanzapine group than in the typical antipsychotic-treated group, both in the sample of patients with prominent positive symptoms and in the sample of agitated patients. Significant differences were also found in BPRS-positive scores, BPRS-negative scores and CGI scores in these two populations.

The other limitation is that in large samples statistically significant differences may have limited clinical importance. However, to exclude this limitation the cut-off level for significance for all analyses was determined, a priori, to be $p = 0.001$. Non-significant *p*-values between 0.05 and 0.001 are also presented in this article. Because of this, the differences of the variables reported in this study can reflect differences that may be clinically meaningful.

Conclusions

Initial 6-month findings indicate that olanzapine provides control in terms of positive, negative, depressive, cognitive and overall symptoms in outpatients treated for schizophrenia. Significantly fewer patients taking olanzapine developed EPS and TD. The prevalence of sexual disorders in this patient population was high. The antipsychotic action of some drugs is associated with sexual dysfunction. Olanzapine had a more favourable side-effect profile than other antipsychotics or risperidone in reducing or eliminating the incidence of adverse effects associated with sexual function. When selecting an antipsychotic treatment for patients, clinicians should consider its safety profile in order to optimise the disease management of the psychotic patient. After 6 months, patients treated with olanzapine in the AMEA region, as used in clinical practice, showed greater improvement in terms of effectiveness of treatment, overall safety and functional status than patients treated with other antipsychotics. Evaluation and reports

will continue prospectively throughout the remainder of the study.

This paper is one of two similar papers reporting aspects of the IC-SOHO Study. The other, 'The Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) Study: 6-month efficacy results from the observational study in the region of Central and Eastern Europe' has been accepted for publication to *Neuropsychiatrie*.

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