The intercontinental schizophrenia outpatient health outcomes study (IC-SOHO): initial 6 month findings of the sample in Latin America

E. Brunner[1]
P. Gargoloff[2]
O. Caro[3]
C. González[4]
E. Landa[5]
C. H. González[6]
A. Barahona[7]
D. Soria[8]
J. Tamayo[9]
J. Rovner[10]
C. Adrianzen[11]
H. Silva[12]
A. Hodge[13]
R. O'Halloran[13]
S. S. M. Assunção[14]
in name of the IC-SOHO study group

[1] Eli Lilly, Canada
[2] Clínica de City Bell Argentina
[3] First Panamerican Hospital Cidra (Puerto Rico)
[4] Hospital Universitario de Caracas Venezuela
[5] Sanatorio San Juan de Dios Zapopan, Jalisco (Mexico)
[6] Centro Médico Imbanaco Cali (Colombia)
[7] Hospital Militar Tegucigalpa (Honduras)
[8] Hospital General Clínica 2 del IMSS Saltillo, Coahuila (Mexico)
[9] Eli Lilly Puerto Rico
[10] Eli Lilly Buenos Aires (Argentina)
[11] Eli Lilly San Isidro-Lima (Peru)
[12] Clínica Psiquiátrica de la Universidad de Chile Santiago (Chile)
[13] Clinical Outocomes and Research Institute Eli Lilly Australia
[14] Clinical Research Physician Eli Lilly. Brasil

The IC-SOHO study was designed to supply information on antipsychotic treatments in the real clinical practice by assessment of a large and diverse sample population with schizophrenia. This document describes the findings of the first 6 months of IC-SOHO in Latin America. To date, this is the largest observational study of its type in this region.

In this observational and prospective study, those outpatients with schizophrenia, who require a change or initiation of antipsychotic medication are hospitalized. Effectiveness was evaluated using the Clinical Global Impression-Seriousness (CGI-S) grading scale. Tolerability was assessed by questionnaires on adverse events and weight measurements. Herein, the comparisons between olanzapine (monotherapy), risperidone (monotherapy) and conventional antipsychotics (monotherapy and combined therapy) are presented.

As a whole, 7,658 patients participated in the IC-SOHO; n = 2,671 from 11 countries of Latin America that were included in this report. At 6 months, the proportion of patients who responded to olanzapine was significantly greater than those who responded to risperidone or conventional antipsychotics ($p < 0.001$). Patients from the olanzapine group had greater improvements in all the symptom domains, including general, positive, negative, depressive and cognitive symptoms in comparison with risperidone ($p < 0.05$) or conventional antipsychotics ($p < 0.001$). Extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) decreased from baseline in the groups treated with olanzapine and risperidone, but increased in the conventional group. Adverse events related with the sexual function were more prominent in the conventional group. Weight gain was observed in each treatment group, although the patients from the olanzapine group had greater weight gain followed by those of risperidone and then by those of conventional antipsychotics.

Our findings in this population of the Latin American sample emulate the results of other studies in different samples, where it was found that olanzapine was more effective and better tolerated than risperidone or conventional antipsychotics.

Key words:
Schizophrenia. Observational study. Olanzapine. Risperidone. Conventional antipsychotics.

Actas Esp Psiquiatr 2006;34(1):16-27

Estudio observacional intercontinental de los resultados de salud en pacientes ambulatorios con esquizofrenia (IC-SOHO): hallazgos iniciales de 6 meses de la muestra

El estudio IC-SOHO se diseñó para aportar información sobre los tratamientos antipsicóticos en la práctica clínica real mediante la evaluación de una población de muestra grande y diversa con esquizofrenia. Este documento describe los hallazgos de los primeros 6 meses del IC-SOHO en Latinoamérica. A la fecha éste es el estudio observacional más grande de su tipo en esta región.

En este estudio observacional y prospectivo se ingresaron aquellos pacientes ambulatorios con esquizofrenia que requirieron un cambio o un inicio de medicación antipsicótica. La efectividad se evaluó utilizando la escala de Calificación de Impresión Clínica Global-Gravedad (CGI-S). La tolerabilidad se evaluó mediante cuestionarios de eventos adversos y mediciones de peso. Se presentan aquí las comparaciones entre olanzapina (monoterapia), risperidona (monoterapia) y antipsicóticos convencionales (monoterapia y terapia combinada).

The present study was conducted under the sponsorship of Eli Lilly and Company (Indianapolis, USA). The authors Brunner, Hodge (until the year 2003), Adrianzen, Rovner, Tamayo, O'Halloran (until the year 2003) and Assunção (until the year 2005) formed a part of the medical group and Research of Eli Lilly and Company.

Correspondence:
Cecilia Adrianzen
Eli Lilly and Company
Las Begonias, 441
Piso 11 San Isidro
Lima (Perú)
E-mail: adrianzen_cecilia@lilly.com

En conjunto, participaron 7.658 pacientes en el IC-SOHO; n = 2.671 provenientes de 11 países de Latinoamérica se incluyeron en este informe. A los 6 meses la proporción de pacientes que respondieron a la olanzapina fue significativamente mayor que los que respondieron a la risperidona o los antipsicóticos convencionales ($p < 0,001$). Los pacientes del grupo de olanzapina tuvieron mejorías mayores en todos los dominios de síntomas, incluyendo los síntomas generales, positivos, negativos, depresivos y cognoscitivos en comparación con la risperidona ($p < 0,05$) o los antipsicóticos convencionales ($p < 0,001$). Los síntomas extrapiramidales (SEP) y la discinesia tardía (DT) disminuyeron desde la línea basal en los grupos tratados con olanzapina y risperidona, pero aumentaron en el grupo convencional. Los efectos adversos relacionados con la función sexual fueron más prominentes en el grupo convencional. Se observó ganancia de peso en cada grupo de tratamiento, aunque los pacientes del grupo de olanzapina aumentaron más de peso, seguidos por los de risperidona y después por los de antipsicóticos convencionales.

Nuestros hallazgos en esta población de muestra latinoamericana emulan los resultados de otros estudios en muestras diferentes, donde se encontró que la olanzapina fue más efectiva y mejor tolerada que la risperidona o los antipsicóticos convencionales.

Palabras clave:
Esquizofrenia. Estudio observacional. Olanzapina. Risperidona. Antipsicóticos convencionales.

INTRODUCTION

The clinical practice guidelines consistently recommend antipsychotic therapy as standard therapy for management of schizophrenia. Until recently, conventional antipsychotic medications were the most common antipsychotics used both in acute as well as maintenance phase of this disease. During the last decade, there was a change towards the use of new generation antipsychotics (NGA), now frequently recommended by the practice guidelines as first line therapy for the treatment of schizophrenia and other psychotic conditions[1].

In Latin America, the conventional agents are still the most commonly prescribed antipsychotics, although it is well-documented that NGA have a wide spectrum of clinical efficacy and are better tolerated than conventional medications[2,3]. Besides providing similar or better efficacy in terms of positive symptoms[4], the NGA are also more effective against negative[5], depressive[6] and cognitive symptoms[7]. Significantly, the NGA reduce the risk of developing adverse EPS and TDs, that continue to be a significant concern regarding long term treatment with conventional antipsychotics[4,8].

Most of the data regarding NGAs come from controlled clinical trials (CCT). These studies are essential to establish efficacy and safety of new medications. However, due to their design, CCT require select populations, that often exclude patients with comorbidities and substance abuse and that have been relatively short and generally are not based in the community[9]. This lack of external validity may limit the translation of the results of the CCTs to the real clinical practice, since they have indirect applicability to the general population of schizophrenia patients[10,11]. Furthermore, the interpretation of CCT results for populations of patients in different parts of the world may be complicated, due to the transcultural and transethnic variations in responses to antipsychotic agents[12].

Ideally, the results of the CCT should be complemented with observational studies, as the IC-SOHO, because observational studies evaluate effectiveness of treatments as used in the real clinical practice[13,14]. The advantages of the observational studies consist in the possibility of studying larger numbers of patients during longer periods under real clinical conditions with minimum inclusion/exclusion criteria. However, to date, most of the observational studies have been insufficient in regards to size and duration and some of them have a retrospective design[15]. Because the retrospective studies are designed after collecting the data, they provide less rigorous conclusions. Thus, prospective observational studies supply more solid observational data to complement the CCT findings.

The intercontinental schizophrenia outpatient health outcomes study (IC-SOHO) is a 3 year prospective observational study, presently on-going, designed to evaluate a large and diverse population in four continents, for 36 months, using a series of simple but valid impact measurements of antipsychotics in schizophrenia treatment. The size of the IC-SOHO study not only permits the analysis of general findings of all the intercontinental sample but also the comparison of intracontinental and intercontinental findings. This document describes the results of the first 6 months of the IC-SOHO study in Latin America. Specifically, this analysis compares the effectiveness of olanzapine with that of risperidone and of the conventional antipsychotic agents prescribed to out-patients with schizophrenia in 11 Latin American countries.

METHODS

Study design and objectives

The IC-SOHO study (study code: F1D-SN-HGJR) is a prospective, global, 3 year, observational study of the antipsychotic medications used to treat schizophrenia. This study has a naturalistic approach and is designed to evaluate clinical, functional results as well as those of quality of life and economic results that reflect real life scenarios. It is also an open study. The medications include all the antipsychotic treatments available and recorded for schizophrenia (that may have differed between countries), with special emphasis on the NGA olanzapine.

Regions and participating countries

The IC-SOHO study is presently being conducted in 27 countries, that include Africa, Asia, Central and Eastern Europe, Latin American and Middle East, with a total of 7,658 participants. Twelve Latin American countries are participating, with a total of 3,804 patients enrolled in this region (Argentina [n = 362], Brazil [n = 1133], Chile [n = 167], Colombia [n = 202], Costa Rica [n = 96], El Salvador [n = 37], Guatemala [n = 81], Honduras [n = 66], Mexico [n = 1067], Peru [n = 99], Puerto Rico [n = 223] and Venezuela [n = 271]). Due to internal policies, the Brazil data could not be included in this analysis. The Brazil results will be reported independently. Enrollment included the dates November 14, 2000 to December 7, 2001, involving 275 Latin American psychiatrists.

Enrollment criteria

At their will, the participating psychiatrists, who were trained in the study procedures, offered hospital admission to patients with clinical diagnosis of schizophrenia (ICD-10 or DSM-IV) who fulfilled the following participation criteria: *a)* having initiated or changed antipsychotic medication for schizophrenia treatment; *b)* presenting with the normal course of care in an out-patient or hospital setting (only when admission was planned to initiate or change the antipsychotic medication, with planned discharge of patient for the course of 2 weeks); *c)* having reached at least 18 years of age, and *d)* not being simultaneously participating in a study that requires a procedure.

Patient consent

To permit the use of their data, the patients (or their legal representative) were asked to provide at least their oral consent. The requirements of written consent were determined by the local regulations in each participating country. The data were obtained during the visits that constituted the normal course of the patient's treatment.

Treatment arms

This study does not follow a random allocation to a treatment group, due to its observational and naturalistic design. Each participating psychiatrist was asked to included patients using an alternative admission structure between two treatment arms, until obtaining a block of 10 (that is, five in each group). The two treatment arms were: *a)* patients who had initiated or changed to olanzapine as their antipsychotic therapy, or *b)* patients who had initiated or changed to any other antipsychotic agent. To assure that the study reflected a naturalistic scenario within each country, the psychiatrists were first instructed to make the treatment decisions independently of the study, applying their standard clinical practice guidelines and then evaluating if the patients were eligible to participate based on the enrolment criteria and the alternative admission structure. Choice of antipsychotic as well as dose prescribed were up to the treating psychiatrist.

Measurement of results

Effectiveness was measured using the grading scale of Clinical Global Impression-Seriousness (CGI-S). The CGI-S scale was adopted[16] to include four additional domains of symptoms (positive, negative, depressive and cognitive symptoms), each one graded from 1 to 7 (1, normal, 7, seriously ill). Responders to treatment were defined as those patients with a general baseline CGI-S grade ≥ 4 that decreased to ≥ 2; or with a general baseline CGI-S ≤ 3 that decreased to ≥ 1. By definition, the patients with a CGI grade of 1 could not be considered responders, but this only occurred with a total of 11 patients included in this analysis. The baseline demographic data of the patients, treatment patterns during the study, prescription of concomitant medications, compliance and tolerability to treatment (evaluated by adverse events questionnaires) were also recorded.

Treatment groups

To compare the results obtained with the individual antipsychotics, 3 treatment groups were established *post hoc* based on the antipsychotic prescribed in the baseline: *a)* olanzapine (monotherapy; n = 1,270); *b)* risperidone (monotherapy; n = 388) and *c)* conventional antipsychotics (monotherapy and combined therapy; n = 510). The treatment groups were established based on the principle of intention to treat, which means that the patients were included in the treatment group to which they were assigned, even when they did not strictly follow this treatment during the rest of the study.

Statistical analysis

Statistical analysis was done using the SAS© program, version 8.2 for Windows™ (SAS Institute, Cary, N.C.). Quantitative variables were described using summarized statistics such as means and standard deviations. Qualitative variables were described using frequencies and percentages. Patients with data lacking were excluded from the pertinent analyses. Differences between the groups treated with olanzapine and risperidone and between the groups of olanzapine and conventional treatment were analyzed using the T test for samples for analysis of quantitative variables or χ^2 tests for the analysis of qualitative variables. Due to the number of comparisons and explanatory nature of this analysis, care should be taken when interpreting statistical significance. Values of $p < 0.05$ will be reported.

RESULTS

Demographic baseline data

Of the 7,658 patients who participated in the general intercontinental region, 2,671 (35%) lived in Latin America. Table 1 shows the demographic data and baseline characteristics of all the Latin American sample population, and specifically the patients who were prescribed olanzapine (monotherapy), risperidone (monotherapy) or conventional antipsychotics (as monotherapy or combined therapy), on admission.

Treatment patterns

In the baseline, 90% of the patients initiated or changed to monotherapy and 10% to a combination of antipsychotics. Conventional antipsychotics were prescribed to 19% of the patients as monotherapy or in combination; haloperidol was the most frequently prescribed conventional antipsychotic. Due to the study design, the most frequently prescribed NGA for monotherapy was olanzapine (48%). Risperidone was the second NGA most commonly prescribed (15% as monotherapy) (table 1).

In the conventional group, monotherapy was prescribed to 82% of the patients and a combination of conventional antipsychotics to 18% on admission. During treatment, 69% remained with monotherapy and 18% more with combined therapy. Most of the patients of the olanzapine (97%) and risperidone (96%) treatment groups remained with monotherapy during the study.

Mean, median and modal dose of olanzapine, risperidone and conventional antipsychotics are indicated in table 2. Median dose of haloperidol (conventional antipsychotic prescribed most frequently) was maintained at 15 mg/day (equivalent to 750 mg of chlorpromazine/day) during the treatment.

Effectiveness

Improvements in effectiveness were observed in each treatment group both at 3 and 6 months (table 3 and fig. 1). The olanzapine group patients showed greater improvement in all the symptom domains, including the general, positive, negative, depressive and cognitive symptoms in comparison with the conventional treatment group patients ($p<0.001$), and in regards to the risperidone group patients ($p<0.05$). In

Table 1 Baseline characteristics of the Latin American region patients

Characteristic	General (n = 2,671)	Olanzapine (n = 1,270)	Risperidone (n = 338)	Conventional (n = 510)
Distribution (%)	100	48	15	19
Gender (% women) (n)	41 (1,095)	42 (523)	42 (162)	46 (234)
Mean ages (years) (SD)	35.8 (12.5)	35.1 (12.6)	35.4 (12.2)	37.3 (12.2)*
Mean BMI (kg/m^2) (SD)	25.3 (4.2)	25.3 (4.3)	25.3 (4.1)	25.2 (4.2)
Without neuroleptics (%) (n)	19 (486)	23 (282)	22 (84)	12 (60)**
Mean duration of diagnosis (years) (SD)	11.2 (10.9)	10.1 (10.7)	10.8 (10.5)	13.2 (11.4)**
Clinical status (mean CGI-S) (SD)				
General symptoms	4.43 (1.14)	4.49 (1.11)	4.34 (1.11)*	4.40 (1.14)
Positive symptoms	4.08 (1.33)	4.08 (1.33)	3.94 (1.26)	4.21 (1.33)
Negative symptoms	4.02 (1.37)	4.07 (1.34)	4.02 (1.25)	3.88 (1.41)*
Depressive symptoms	3.40 (1.49)	3.50 (1.51)	3.43 (1.39)	3.09 (1.45)**
Cognitive symptoms	3.87 (1.42)	3.87 (1.43)	3.79 (1.38)	3.87 (1.45)
Adverse events (%) (n)				
Extrapyramidal symptoms	43 (1,135)	41 (511)	49 (189)*	42 (212)
Tardive dyskinesia	8 (221)	7 (92)	8 (31)	9 (43)
Involved in a relationship (%) (n)	28 (705)	30 (363)	27 (99)	25 (123)*
Involved in social activities[a] (%) (n)	57 (1,499)	57 (704)	64 (242)	51 (255)
Employed with salary[a] (%) (n)	17 (444)	18 (222)	19 (74)	16 (80)
Living independently[a] (%) (n)	23 (614)	23 (298)	25 (98)	25 (127)
Health status[b] (mean) (SD)	51 (22)	49 (22)	49 (21)	53 (22)*
Suicide attempt[c] (%) (n)	9.3 (245)	10 (127)	9 (35)	7 (33)*

*$p<0.05$-0.001 compared with olanzapine; **$p<0.001$ compared with olanzapine. [a] In the 4 weeks prior to baseline. [b] Perspective of patient at visit, according to Visual Analogue scale 0-100 for EuroQol EQ-5D, where 100 is the best possible. [c] In the 6 months prior to baseline.

Table 2 Oral doses of olanzapine, risperidone and conventional antipsychotics prescribed at each visit

Time point and measurement	Olanzapine (n = 1,270)**	Risperidone (n = 338)**	Conventional* (n = 510)**
Baseline			
Mean dose (mg/day) (SD)	9.7 (3.8)	3.9 (1.8)	408.4 (424.2)
Median	10.0	4.0	300.0
Mode	10.0	4.0	300.0
3 months			
Mean dose (mg/day) (SD)	10.3 (4.2)	4.2 (2.0)	380.1 (394.7)
Median	10.0	4.0	250.0
Mode	10.0	6.0	300.0
6 months			
Mean dose (mg/day) (SD)	10.2 (4.3)	4.3 (2.0)	360.4 (393.7)
Median	10.0	4.0	240.0
Mode	10.0	6.0	100.0

*Reported as equivalents of chlorpromazine; **n represents number of patients in each treatment group. The real numbers of patients who contribute to the dose calculations may be lower, due to lacking data and patients who do not continue with the originally prescribed medication.

addition, there was a significantly greater proportion of patients considered as responders in the olanzapine group compared with that of risperidone or of the conventional antipsychotics ($p<0.001$) (fig. 2).

Tolerability

Adverse events related with motor function

At 3 and 6 months, presence of EPS was significantly less in the olanzapine group in comparison with that of the risperidone or conventional antipsychotics groups ($p<0.001$) (fig. 3). In addition, a significantly lower proportion of patients from the olanzapine group developed emergent EPS from treatment and a significantly greater proportion of them recovered preexisting EPS regarding the risperidone and conventional treatment groups ($p<0.001$).

Significantly more patients from the conventional group showed TD at 3 and 6 months in comparison with those of the olanzapine group ($p<0.001$). There was a lower proportion of new TD cases in the olanzapine group in comparison with the conventional treatment group. There were no differences between treatments with olanzapine and risperidone in regards to the TD incidence in any observation point.

Adverse events related with sexual function and hyperprolactinemia

The proportion of patients who reported loss of libido and impotence/sexual dysfunction were less in the olanzapine group than in the risperidone and conventional groups, both at 3 and 6 months (table 4). Treatment with conventional antipsychotics resulted in a greater proportion of patients with adverse events related with increase of prolactin (amenorrhea, galactorrhea and gynecomastia). This was significant in regards to olanzapine ($p<0.001$). A lower proportion of female patients in the olanzapine group reported amenorrhea at 3 and 6 months in comparison with the risperidone group.

Weight changes

At six months, patients with low weight (BMI < 18.5 kg/m^2) at baseline gained more weight in comparison with overweight (BMI $\geq 25/<30$ kg/m^2) or obese patients (BMI ≥ 30 kg/m^2) at baseline. This was true for each treatment group. In general, patients in the olanzapine group gained more weight (3.14 ± 5.66 kg) in comparison with those of the risperidone group (2.04 ± 5.71 kg) ($p=0.003$) or the conventional one (1.24 ± 4.36 kg) ($p<0.001$). A greater proportion of patients from the olanzapine group gained $>7\%$ of the baseline weight (31%) compared to that of risperidone (22%) ($p=0.002$) and conventional antipsychotics (16%) ($p<0.001$).

Concomitant medications

Concomitant drug prescription decreased from baseline in all the patient groups (fig. 4). In baseline, a significantly lower proportion of anticholinergics was prescribed to the olanzapine group patients than to those of the risperidone or conventional group ($p<0.001$). At 6 months, anticholinergics were prescribed significantly more frequently to patients in the risperidone or conventional group in comparison with those of olanzapine ($p<0.001$). Other concomitant drugs (including antidepressants, anxiolytics/hypnotics and mood stabilizer agents) were also prescribed to a greater proportion of patients from the conventional group in comparison with the olanzapine group ($p=0.002$).

Compliance

The patient's perception regarding compliance indicated that 86%, 86% and 75% respectively of the patients from the olanzapine, risperidone and conventional groups complied with taking their medication almost all the time during the 6 month period. This difference was significant in comparison of olanzapine with conventional antipsychotics ($p< 0.001$). There was a high level of association between the perception of the patient and psychiatrist in regards to compliance in each time point ($p<0.001$, weighted kappa test).

Table 3 Clinical status (CGI-S[a]) of patients prescribed olanzapine, risperidone and conventional antipsychotics after 3 and 6 months of treatment

Symptom domain	3 months		Change at 3 months from baseline		p value[b]	6 months		Change at 6 months from baseline		p value[b]
	Mean	SD	Mean	SD		Mean	SD	Mean	SD	
General symptoms										
Olanzapine	3.12	1.12	−1.35	1.20		2.75	1.14	−1.71	1.36	
Risperidone	3.18	1.01	−1.14	1.17	0.0034[c]	2.86	1.02	−1.45	1.33	0.0023[c]
Conventional	3.52	1.09	−0.83	1.15	<0.0001[d]	3.30	1.15	−1.11	1.23	<0.0001[d]
Positive symptoms										
Olanzapine	2.64	1.23	−1.42	1.38		2.27	1.16	−1.75	1.52	
Risperidone	2.71	1.15	−1.21	1.30	0.0117[c]	2.41	1.12	−1.50	1.39	0.0063[c]
Conventional	3.03	1.27	−1.15	1.31	0.0002[d]	2.74	1.21	−1.45	1.42	0.0006[d]
Negative symptoms										
Olanzapine	2.95	1.21	−1.11	1.29		2.56	1.16	−1.47	1.43	
Risperidone	3.09	1.14	−0.92	1.22	0.0144[c]	2.76	1.10	−1.24	1.30	0.0095[c]
Conventional	3.31	1.31	−0.55	1.30	<0.0001[d]	3.06	1.22	−0.81	1.27	<0.0001[d]
Depressive symptoms										
Olanzapine	2.59	1.24	−0.93	1.40		2.31	1.21	−1.24	1.50	
Risperidone	2.70	1.16	−0.74	1.24	0.0208[c]	2.48	1.19	−0.97	1.43	0.0030[c]
Conventional	2.60	1.28	−0.44	1.21	<0.0001[d]	2.54	1.25	−0.58	1.33	<0.0001[d]
Cognitive symptoms										
Olanzapine	2.85	1.27	−1.00	1.33		2.54	1.21	−1.27	1.46	
Risperidone	2.97	1.19	−0.81	1.21	0.0192[c]	2.71	1.14	−1.09	1.39	0.0448[c]
Conventional	3.28	1.35	−0.59	1.23	<0.0001[d]	3.11	1.32	−0.79	1.33	<0.0001[d]

[a] CGI–S scale of score on Clinical Global Impression -Seriousness (1–7). [b] *t* test of two samples. [c] Change from baseline for olanzapine vs risperidone. [d] Change from baseline for olanzapine vs conventional antipsychotics.

Discussion

As far as we know, this is the largest prospective observational study that investigates effectiveness of antipsychotics as treatments for schizophrenia in real clinical scenarios in Latin America. Comparisons between olanzapine and conventional antipsychotics and olanzapine and risperidone are especially important in this region. Our results have demonstrated that NGA, especially olanzapine, are more effective and better tolerated than conventional antipsychotics in this sample. On the other hand, when compared with risperidone, olanzapine showed a significantly greater proportion of patients who responded to the therapy and significantly larger benefits, as is shown in our primary tolerability measurements.

Effectiveness

In our study, improvement of most of the clinical symptoms of the Latin American out-patients was observed to be significantly greater in the olanzapine treatment group compared to the risperidone and conventional antipsychotics. The differences observed were found in the observation made up to 3 months and were maintained in the 6 month visit, which was the last of the initial period analyzed in this document. Our observations complement the previous findings of efficacy of the CCTs and support the superiority of olanzapine regarding the conventional antipsychotics and other NGAs in many regions, including Latin America[17-20].

In comparison with the conventional antipsychotics, olanzapine significantly improved clinical effectiveness in all the symptom categories. In support of previous findings, olanzapine was better in the treatment of positive symptoms than conventional agents[21,22]. It is important that an antipsychotic agent can improve all the symptoms of the pathological state, such as negative, depressive and cognitive symptoms that may coexist with the positive symptoms and become clearer when the positive symptoms are under control[23,24,25]. As in other reports, we found that olanzapine was superior to conventional agents in the treatment of negative

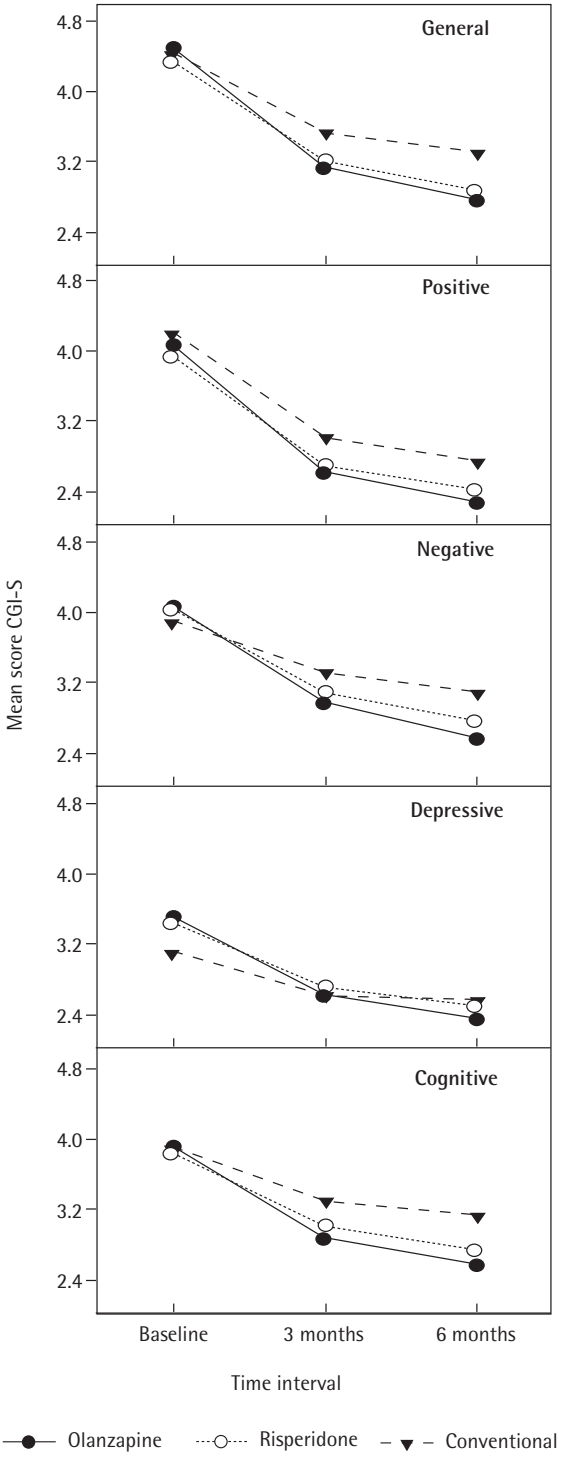

Figure 1 *Clinical status (CGI-S) of the patients who were prescribed olanzapine, risperidone and conventional antipsychotics after 3 and 6 months of treatment.*

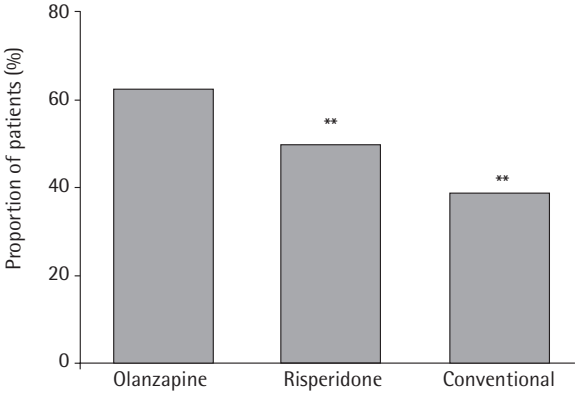

Figure 2 *Patients who responded to therapy at 6 months. The reactive patients were defined as those with a CGI-S socre at baseline of ≥ 4, who subsequently decreased to ≥ 2 at months, with baseline CGI-S ≤ 3, who subsequently decreased to ≥ 1 at 6 months; ** p< 0.001 compared to olanzapine.*

symptoms[23,26]. Negative symptoms, depression and cognitive deficiencies are associated with decreased drug compliance, and also show negative repercussions on the interpersonal, social and occupational relationships, prognosis and possibility of rehabilitation and, even on suicide[27-29]. Thus, costs of inadequate treatment of all the symptom domains are high.

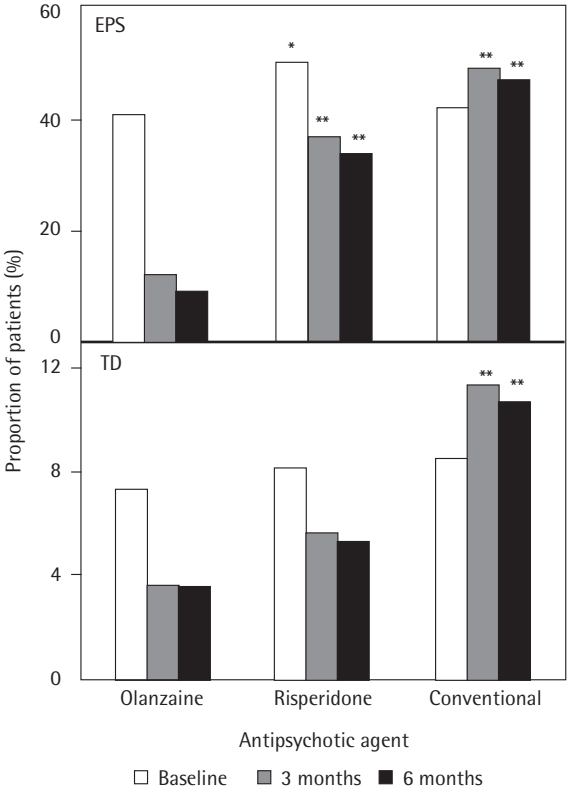

Figure 3 *Presence of EPS and TD at baseline, and after 3 and 6 months of treatment with olanzapine, risperidone and conventional antipsychotics. * p = 0.003 compared with olanzapine; ** p < 0.001 compared with olanzapine.*

Table 4 Adverse events related with sexual function and hyperprolactinemia at baseline and after 3 and 6 months and with body weight at baseline and after 6 months of treatment with olanzapine, risperidone and conventional antipsychotics

Adverse events	Olanzapine (n = 1,270)	Risperidone (n = 338)	Conventional (n = 510)
Loss of libido			
Baseline (%) (n)	49 (550)	52 (180)	46 (213)
3 months (%) (n)	36 (388)	46 (159)**	46 (204)**
6 months (%) (n)	31 (305)	49 (158)**	50 (196)**
Impotence/sexual dysfunction			
Baseline (%) (n)	34 (330)	34 (104)	30 (118)
3 months (%) (n)	21 (204)	31 (94)**	33 (118)**
6 months (%) (n)	20 (170)	28 (80)*	33 (106)**
Amenorrhea/menstrual disorders[a]			
Baseline (%) (n)	28 (121)	30 (42)	32 (63
3 months (%) (n)	17 (71)	24 (34)	33 (63)**
6 months (%) (n)	15 (64)	23 (34)*	32 (56)**
Galactorrhea			
Baseline (%) (n)	5 (41)	5 (14)	6 (20)
3 months (%) (n)	2 (18)	4 (10)	8 (24)**
6 months (%) (n)	2 (14)	2 (5)	6 (17)**
Gynecomastia			
Baseline (%) (n)	4 (40)	3 (9)	5 (19)
3 months (%) (n)	3 (23)	2 (4)	9 (30)**
6 months (%) (n)	3 (23)	4 (10)	9 (28)**
Weight alterations			
BMI at baseline (kg/m^2) (SD)	25.3 (4,3)	25.3 (4.1)	25.2 (4.2)
Mean weight alteration at 6 months (kg) (SD)	3.14 (5.66)	2.04 (5.71)[b]	1.24 (4.36)[c]
Patients (%) who gained weight > 7 %	31	22[d]	16[c]

* $p < 0.05$-0.001 compared with olanzapine; ** $p < 0,001$ compared with olanzapine. [a] Only female patients; [b] $p = 0.003$ compared with olanzapine; [c] $p < 0.001$ compared with olanzapine; [d] $p = 0.002$ compared with olanzapine.

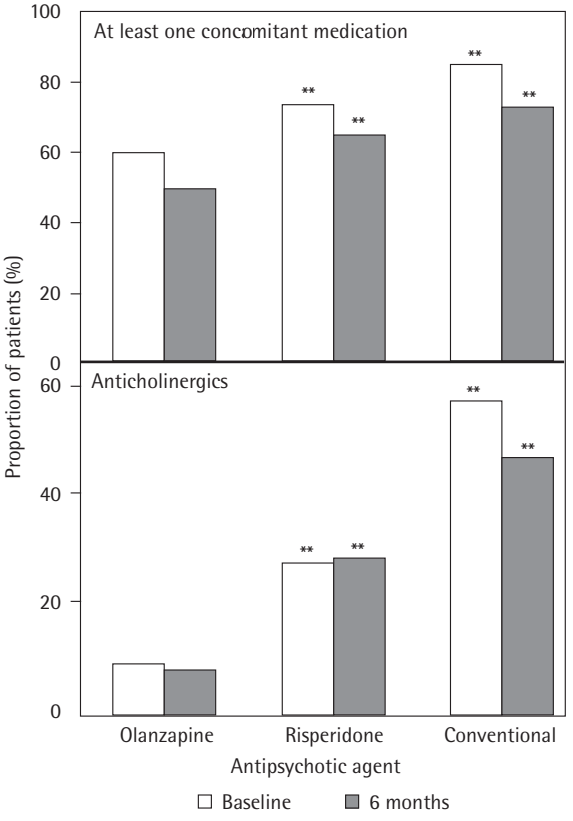

Figure 4 *Concomitant medications prescribed at baseline and at 6 months. **p < 0.001 compared with olanzapine.*

Comparing both NGA, a significantly greater proportion of patients responded to treatment with olanzapine (62 %) than with risperidone (49 %). Equally, patients treated with olanzapine had greater clinical improvements in all symptom domains compared with risperidone. Several CCT have demonstrated more efficacy of olanzapine regarding risperidone in the reduction of seriousness of symptoms, including several symptom domains[18,20,25,30]. However, other CCT have not shown a difference between these agents in several efficacy measurements and, in fact, some CCT have shown greater clinical improvements with risperidone[15,31]. The reason for these different results is not clear. Possibly, the risperidone dose used in some studies has not been sufficient to reach maximum benefits. In our study, the risperidone dose prescribed most commonly was maintained between 4 and 6 mg/day during the 6 months, which is consistent with the recommendations for the optimum response[32].

Tolerability

The EPS incidence decreased regarding baseline values in the olanzapine and risperidone treatment groups while they increased in the conventional one. This finding agrees with many previous studies in which it was reported that conventional antipsychotics show a strong tendency to induce EPS[33,34]. This tendency may be due to the fact that such agents have almost no anticholinergic activity associated with their action mechanism. In our study, the EPS incidence increased in spite of the fact that 56 % of the patients who took conventional medications were also prescribed anticholinergics in baseline, perhaps to minimize the develop-

ment of EPS. Our findings also support previous safety data of olanzapine, which has been consistently observed to produce significantly lower incidences of EPS compared with conventional antipsychotics[34-36] and risperidone[18,37].

We have found that a lower proportion of patients treated with risperidone had EPS compared with those receiving conventional antipsychotics. However, risperidone was significantly inferior to olanzapine in this measurement. One characteristic of the NGAs is their reduced tendency to cause EPS adverse events, although there are differences between the NGAs regarding their adverse events profile. In general, risperidone tends to overlap with the conventional antipsychotics in their risk, depending on dose, of inducing EPS and also probably of inducing TD[38]. Risperidone induces less EPS when administered in 4-8 mg/day dose[39], and even above 10 mg/day, risperidone induces EPS as frequently as conventional antipsychotics[40]. The mean dose of risperidone in this study (4-6 mg/day) is close to the lower threshold expected to cause an increase of EPS. However, risperidone causes EPS in a significantly higher proportion of patients compared with olanzapine.

Our descriptive data on the baseline observation verify that concomitant medications are commonly prescribed with antipsychotics to schizophrenia patients. This may be partially due to the complexity and extension of the disease symptoms in addition to the adverse events profile of some antipsychotic medications. Anticholinergics include a large part of the prescriptions of concomitant medications, perhaps as a reflection of the high presence of EPS and TD. The lowest rates of anticholinergic prescription were observed at baseline in the olanzapine treatment group. This may be indicative of the low expectation of emergent EPS and TD of treatment with olanzapine. Since anticholinergics are more commonly co-prescribed with conventional antipsychotics or EPS inductors[41], it is not surprising that 56% of the patients treated with conventional antipsychotics have been prescribed these medications. It is outstanding that the prescription of anticholinergics in the conventional treatment group decreased at 6 months and that this reduction coincided with an increase in both EPS and TD of this group. Concomitant anticholingerics were prescribed to significantly more patients of the risperidone group at 6 months and the presence of adverse events associated with motor function was proportionally higher in that group in comparison with that of olanzapine. Furthermore, anticholinergics were prescribed less frequently to patients treated with olanzapine than to other patients at 6 months, which suggests that the motor efficacy and safety profile observed with olanzapine was probably due to olanzapine alone, without increase due to concomitant medications.

Sexual dysfunction

It was observed in the baseline description of the patients that the adverse events related with sexual functioning were high, however they decreased more with time in the olanzapine group versus the other treatments. This may be a reflection of the improvements in the clinical state of these patients. However, it is possible that olanzapine normalizes preexisting hyperprolactinemia[42], even though the prolactin levels were not measured in this study. Our observations demonstrate that the adverse events associated with sexual function were greater after treatment with conventional antipsychotics and risperidone. This is consistent with the findings in the literature, in the sense that conventional antipsychotics[43,44] and risperidone[44,45] consistently elevate plasma prolactactin levels and, as a probable consequence, may cause problems in sexual function.

Weight change

It is well documented that several antipsychotic medications are associated with weight changes[46]. This may be intrinsically related with their action mechanism[47]. According to the available literature, we report that patients who received olanzapine gained more weight during this study, followed by those with risperidone and then by those with conventional antipsychotics. However, the magnitude of the weight gain recorded with each treatment in this population was inferior to that reported for the CCTs[48-50].

The clinical relevance of weight gain becomes important with long term antipsychotic therapy since the greatest weight gain occurs during the first months of treatment. Especially in the case of olanzapine, this has been shown to have a tendency to leveling out over time[48]. Our results regarding olanzapine may well represent the greatest part of the weight gain due to exposition to an antipsychotic that will be recorded for this treatment during all the study.

Limitations of the present study and observational studies

The observational studies have several limitations, mainly related with internal validity. These are, for example, open character of the study, that leads to potential bias; open dosing; lack of randomization and control group; heterogeneous populations, that make attribution of causal relationships difficult, potential of less reporting of adverse events compared with the CCTs and frequent use of concomitant medications. Recognizing these inherent difficulties, the present study attempted to maximize internal validity through its design, coverage, large sample size (with substantial power to detect the differences) and its duration. External validity was achieved by minimizing the restrictive enrollment criteria and treatment intervention. The resulting measurements were chosen based on simplicity and facility of use so they reflect the clinical practice in normal circumstances. The international nature of IC-SOHO permitted enrolment of a large variety of patients from different backgrounds, countries, geographies and social levels. This contributed to the knowledge of this disease in areas where information is limited, such as Latin America. Psychiatrists prescribed antipsychotics according to their normal practice

standard and the antipsychotic doses recorded in this study were in agreement with the present international guidelines[46]. We found that a high proportion of patients continued with the originally prescribed medication, with high level of reported compliance and that fluctuations in doses were minimum within each treatment group. All these factors reinforce more the validity and applicability of results to the patients of this region. Thus, they supply useful, relevant and easily interpretable information for Latin American psychiatrists. We recognize that the design of the present study had a larger number of patients in the olanzapine group. From a statistical perspective, this could minimize the random error for the calculations in the olanzapine group. We do not expect it to create a systematic error (bias). However, there is a greater probability of detecting significant differences between the olanzapine group and the other treatment groups. It is important to mention that, given the large number of comparisons done, the minimum p value of significance reported of 0.05 or less could have limited clinical relevance. The reader is advised to use his/her clinical opinion to interpret those differences reported as significant.

Ethnical differences

Although antipsychotic medications are effective through cultural and ethnic limits, anecdotic reports have suggested that Hispanic patients (originating from Latin America) require significantly lower doses of antipsychotic agents to obtain clinical response in comparison with patients of the white race[51,52]. Although the race of the patients included was not systematically recorded and statistical tests were not conducted, we found that the mean dose of olanzapine prescribed at baseline in the Latin American region was similar to the mean dose prescribed in our intercontinental sample. However, a higher mean dose of risperidone was prescribed in comparison with the intercontinental sample. The presence of EPS was similar in treatment with olanzapine, both in the intercontinental and Latin American region while the presence of EPS was comparatively higher during treatment with risperidone in Latin America in comparison with the intercontinental sample. This could be explained by the greater mean dose prescribed. Efficacy and safety of olanzapine have been previously demonstrated in Latin American patients[19,53], and it has been demonstrated that olanzapine successfully reduces haloperidol induced EPSs in these patients[53].

Conclusion

Our observations confirm the findings that the NGA confer benefits that are not always reachable with conventional antipsychotics, especially in terms of control of schizophrenia symptoms and lower incidence of adverse events. Based on our results to date, we conclude that olanzapine is more effective than conventional antipsychotics or risperidone in this Latin American population. Furthermore, it was found that olanzapine is significantly superior to conventional antipsychotics or risperidone in terms of the proportion of patients responding to treatment and in some measurements of tolerability such as the EPSs. Our findings grant maintained support to the role of olanzapine in the reduction of many of the deficits associated with schizophrenia, establishing a clear argument for its use as first line treatment in Latin America.

ACKNOWLEDGEMENTS

This study was supports by a research grant from Eli Lilly and Company. The IC-SOHO study team wants to express their acknowledgment to the following investigators of the Latin American region. *Argentina:* J. C. Abad, H. Battaglia, A. Cortijo, G. Dorado, M. Gagliardi, R. Galeno, G. G. Bonetto, A. Godino, E. Guzzo, F. M. Riera, G. A. Panelo, W. Perinot, G. Petracca, O. R. Rech, A. Rotbart, E. Suárez, J. Travella, R. Velasco, J. Zarra, M. Halberg, E. O. Frágola, M. Holzer, J. J. H. Vilapriño, M. Vilapriño, E. Gris. *Chile:* A. Cuevas, G. Gabler, A. Gazmuri, C. Medina, R. Hormilla, C. Mourges, R. Nachar, S. Zamora, D. Holmgren, P. Arancibia, P. Rioseco, A. Etcheberrigaray, A. Armijo, W. Torres. *Colombia:* D. Toledo, M. Garzón, R. Alarcón, C. González, C. Arango, G. J. López, L. A. Valencia, H. Molinello, R. Haydar, F. Navarro, S. Conde, R. de la Espriella, C. Chain, D. Quintero, J. Palacios. *Costa Rica:* R. Ramírez, E. Abarca, C.L.P. Desanti. El Salvador: C. Padilla, C. Escalante, R. Cornejo, M. M. Peña, J. M. Fortín, J. M. Fortin. *Guatemala:* I. Salazar, N. Ortiz, J. Corrales, A. Saravia T., F. Javier R., M. C. Ruiz. *Honduras:* A. Reyes, D. Herrera. *Mexico:* F. R. Ponce, J. A. Valdez, M. de los A. S. Valis, P. J. V. Fragoso, L. D. Castro, A. R. Castillo, S. G. Valadez, F. G. Rodríguez, E. G. G. Guzmán, J. A. Gasca, S. S. Casares, H. L. Tapia, R. V. Valenzuela, A. M. Salazar, J. B. C. García, M. H. Estrella, A. I. Gómez, L. R. Gutiérrez, V. G. Aranda, B. de G. Gómez, C. B. Arzac, G. Pruneda, G. A. D. de Medina, J. N. Ramos, M. M. Serratos, B. Fernández, L. D. P. Beltrán, M. L. Gómez, E. F. Greenhouse, E. M. Minor, F. P. Beltrán, M. A. M. Duarte, L. M. Zamora, C. C. Caballero, M. F. Moncayo, J. A. Orueta, L. V. Canto, R. Briones, F. de J. T. Peniche, M. A. V. Erosa, A. Rosado, U. Solís, A. Lugo, E. L. Pineda, J. B.Méndez, R. I. Mares, A. L. Rentería, G. C. Garza, G. Cuevas, R. G. Jaramillo, J. J. Flores, J. G. Garza, R. Mahuad, R. M. Villarreal, J. Sordia, R. R. I. Álvarez, R. A. Velázquez, H. R. Hernández, J. F. González, O. A. Pardo, A. F. Hernández, L. G. A. Montes, S. J. Torres, D. A. S. Anguiano, J. A. R. Aldape, J. C. M. Turcios, E. H. Malpica, G. T. Paniagua, B. M. Castellanos, D. H. Guzmán, F. G. Sandoval, A. del P. R. López, V. M. R. Barrios, L. T. Rivero, P. T. Tlamaxco, J. G. del Valle, G. L. Cerón, O. C. Ceja, E. E. Carrera, J. G. M. García, C. E. V. Flores, A. N. Caraveo, G. A. Espinoza, M. A. Galindo, M. C. Herrera, Pérez, C. A. Rivera, J. Lomelí, G. C. Valencia, J. N. A. Hernández, J. L. Camacho, A. N. Serrano, R. M. Gaxiola, E. L. Fournais, C. R. del Alba, S. N. Leal, M. C. A. Medina, H. G. Rábago, M. C. Torres, A. H. Soto, J. Q. Cardiel, R. M. Dávalos, J. N. A. Hernández, J. L. Camacho, A. N. Serrano, R. M. Gaxiola. *Peru:* P. Adán, R. Gastaiburu, H. Zavalaga, I. Aspilcueta, J. Cabrejos. *Puerto Rico:* M. Vargas, L. Príncipe, P. Oyola, J. Agosto, L. Es-

cabí, M. Woodburry, C. Sanz, I. Franceschi, R. Báez, L. Chahin, M. Sánchez, J. León, M. Brignoni, C. Padilla, D. Vega, S. Johnson, G. Tejedor, J. Valentin, R. Coira, F. Entenza, J. Ramos, G. Acevedo, M. Santos, A. Fortuño, C. de Jesús, E. del Valle, M. Pujols, R. Brignoni. *Venezuela:* D. Martínez, G. Rodríguez, J. A. Jiménez, L. la Font, H. L. Borges, C. Carrillo, N. Pacheco, M. Sánchez, A. Zambrano, N. Andrade, M. M. Fuenmayor, L. López, A. Pérez, C. González, R. E. Hernández, A. Mobilli, B. Canabal, L. Madrid, F. Rivero, G. Rodríguez.

REFERENCES

1. Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association. Am J Psychiatry 1997; 154:1-63.
2. Tarsy D, Baldessarini RJ, Tarazi FI. Effects of newer antipsychotics on extrapyramidal function. CNS Drugs 2002;16:23-45.
3. Tandon R, Jibson MD. Efficacy of newer generation antipsychotics in the treatment of schizophrenia. Psychoneuroendocrinology 2003;28 Suppl. 1:9-26.
4. Leucht S, Pitschel-Walz G, Abraham D. Efficacy and extrapyramidal side-effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo. A meta-analysis of randomized controlled trials. Schizophr Res 1999;35:51-68.
5. Balestrieri M, Vampini C, Bellantuono C. Efficacy and safety of novel antipsychotics: a critical review. Hum Psychopharmacol 2000;15:499-512.
6. Kennedy A, Jain S, Vinogradov S. Atypical antipsychotics for schizophrenia: their collective role and comparative profiles. Formulary 2001;36:500-17.
7. Meltzer HY, McGurk SR. The effects of clozapine, risperidone, and olanzapine on cognitive function in schizophrenia. Schizophr Bulletin 1999;25:233-55.
8. Schillevoort I, de Boer A, Herings RM, et al. Risk of extrapyramidal syndromes with haloperidol, risperidone, or olanzapine. Ann Pharmacother 2001;35:1517-22.
9. Thornley B, Adams C. Content and quality of 2000 controlled trials in schizophrenia over 50 years. BMJ 1998;317:1181-4.
10. Concato J, Shah N, Horwitz RI. Randomized, controlled trials, observational studies, and the hierarchy of research designs. N Engl J Med 2000;342:1887-92.
11. Benson K, Hartz AJ. A comparison of observational studies and randomized, controlled trials. N Engl J Med 2000;342: 1878-86.
12. Emsley RA, Roberts MC, Rataemane S. Ethnicity and treatment response in schizophrenia: a comparison of 3 ethnic groups. J Clin Psychiatry 2002;63:9-14.
13. Sacristán JA, Soto J, Galende I. A review of methodologies for assessing drug effectiveness and a new proposal: randomized database studies. Clin Ther 1997;19:1510-7.
14. Black N. Why we need observational studies to evaluate the effectiveness of health care. BMJ 1996;312:1215-8.
15. Kasper S, Rosillon D, Duchesne I. Risperidone olanzapine drug outcomes studies in schizophrenia (RODOS): efficacy and tolerability results of an international naturalistic study. Int Clin Psychopharmacol 2001;16:179-87.
16. Haro JM, Kamath SA, Ochoa S. The Clinical Global Impression-Schizophrenia scale: a simple instrument to measure the diversity of symptoms present in schizophrenia. Acta Psychiatr Scand Suppl 2003;16-23.
17. Tollefson GD, Beasley CM Jr, Tran PV, Street JS, Krueger JA, Tamura RN, et al. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an International Collaborative Trial. Am J Psychiatry 1997;154:457-65.
18. Tran PV, Hamilton SH, Kuntz AJ, Potvin JH, Andersen SW, Beasley C Jr, et al. Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders. J Clin Psychopharmacol 1997;17:407-18.
19. Palmer CS, Brunner E, Ruiz-Flores LG. A cost-effectiveness clinical decision analysis model for treatment of schizophrenia. Arch Med Res 2002;33:572-80.
20. Gureje O, Miles W, Keks N. Olanzapine vs risperidone in the management of schizophrenia: a randomized double-blind trial in Australia and New Zealand. Schizophr Res 2003;61:303-14.
21. Beasley CM Jr, Hamilton SH, Crawford AM, Dellva MA, Tollefson GD, Tran PV, et al. Olanzapine versus haloperidol: acute phase results of the international double-blind olanzapine trial. European Neuropsychopharmacology 1997;7:125-37.
22. Gómez JC, Crawford AMK. Superior efficacy of olanzapine over haloperidol: Analysis of patients with schizophrenia from a multicenter international trial. J Clin Psychiatry 2001;62(Suppl. 2): 6-11.
23. Tollefson GD, Sanger TM. Negative symptoms: a path analytic approach to a double-blind, placebo- and haloperidol-controlled clinical trial with olanzapine. Am J Psychiatry 1997;154: 466-74.
24. Tollefson GD, Sanger TM, Lu Y, Thieme ME. Depressive signs and symptoms in schizophrenia: a prospective blinded trial of olanzapine and haloperidol. Arch Gen Psychiatry 1998; 55:250-8.
25. Purdon SE, Jones BDW, Stip E. Neuropsychological change in early phase schizophrenia during 12 months of treatment with olanzapine, risperidone, or haloperidol. The Canadian Collaborative Group for research in schizophrenia. Arch Gen Psychiatry 2000;57:249-58.
26. Beasley CM Jr, Tollefson G, Tran P, Satterlee W, Sanger T, Hamilton S. Olanzapine versus placebo and haloperidol. Acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 1996;14:111-23.
27. García-Cabeza I, Gómez JC, Sacristán JA. Subjective response to antipsychotic treatment and compliance in schizophrenia. A naturalistic study comparing olanzapine, risperidone and haloperidol (EFESO Study). BMC Psychiatry 2001;1:7.
28. Hamilton SH, Edgell ET, Revicki DA. Functional outcomes in schizophrenia: a comparison of olanzapine and haloperidol in a European sample. Int Clin Psychopharmacol 2000;15:245-55.
29. Keck PE Jr, Strakowski SM, McElroy SL. The efficacy of atypical antipsychotics in the treatment of depressive symptoms, hostility, and suicidality in patients with schizophrenia. J Clin Psychiatry 2000;61 Suppl. 3: 4-9
30. Tollefson GD, Andersen SW, Tran PV. The course of depressive symptoms in predicting relapse in schizophrenia: a double-blind, randomized comparison of olanzapine and risperidone. Biological Psychiatry 1999;46:365-73.

31. Conley RR, Mahmoud RA. Randomized double-blind study of risperidone and olanzapine in the treatment of schizophrenia or schizoaffective disorder. Am J Psychiatry 2001; 158:765-74.
32. Williams R. Optimal dosing with risperidone: Updated recommendations. J Clin Psychiatry 2001;62:282-9.
33. Schillevoort I, de Boer A, Herings RM. Risk of extrapyramidal syndromes with haloperidol, risperidone, or olanzapine. Ann Pharmacother 2001;35:1517-22.
34. Tran PV, Dellva MA, Tollefson GD. Extrapyramidal symptoms and tolerability of olanzapine versus haloperidol in the acute treatment of schizophrenia. J Clin Psychiatry 1997;58: 205-11.
35. Tollefson GD, Beasley CM Jr, Tran PV. Olanzapine versus haloperidol in the treatment of schizophrenia and schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997;154:457-65.
36. Gómez JC, Sacristán JA, Hernández J. The safety of olanzapine compared with other antipsychotic drugs: results of an observational prospective study in patients with schizophrenia (EFESO Study). Pharmacoepidemiologic Study of Olanzapine in Schizophrenia. J Clin Psychiatry 2000;61:335-343.
37. Bhana N, Foster RH, Olney R, Plosker GL. Olanzapine: an updated review of its use in the management of schizophrenia. Drugs 2001;61:111-61.
38. Tarsy D, Baldessarini RJ, Tarazi FI. Effects of newer antipsychotics on extrapyramidal function. CNS Drugs 2002;16:23-45.
39. Balestrieri M, Vampini C, Bellantuono C. Efficacy and safety of novel antipsychotics: a critical review. Hum Psychopharmacol 2000;15:499-512.
40. Stip E. Novel antipsychotics: issues and controversies. Typicality of atypical antipsychotics. J Psychiatry Neurosci 2000;25:137-53.
41. Sacristán JA, Gómez JC, Montejo AL. Doses of olanzapine, risperidone, and haloperidol used in clinical practice: results of a prospective pharmacoepidemiologic study. EFESO Study Group. Estudio Farmacoepidemiologico en la esquizofrenia con Olanzapina. Clin Ther 2000;22:583-99.
42. Kinon BJ, Liu HC, Ahl J. A prospective randomized trial of olanzapine in reduction of neuroleptic-induced hyperprolactinemia in schizophrenia. October 5-9. Poster. European College on Schizophrenia Research (ECNP). Barcelona, Spain, 2002.
43. Cutler AJ. Sexual dysfunction and antipsychotic treatment. Psychoneuroendocrinology 2003;28(Suppl. 1):69-82.
44. Kinon BJ, Gilmore JA, Liu H. Prevalence of hyperprolactinemia in schizophrenic patients treated with conventional antipsychotic medications or risperidone. Psychoneuroendocrinology 2003;28(Suppl. 2):55-68.
45. Huang ML, van Peer A, Woestenborghs R. Pharmacokinetics of the novel antipsychotic agent risperidone and the prolactin response in healthy subjects. Clin Pharmacol Ther 1993;54:257-68.
46. Practice guideline for the treatment of patients with schizophrenia. American Psychiatric Association. Am J Psychiatry 1997; 154:1-63.
47. Casey DE, Zorn SH. The pharmacology of weight gain with antipsychotics. J Clin Psychiatry 2001;62(Suppl. 7):4-10.
48. Kinon BJ, Basson BR, Gilmore JA. Long-term olanzapine treatment: weight change and weight-related health factors in schizophrenia. J Clin Psychiatry 2001;62:92-100.
49. Czobor P, Volavka J, Sheitman B. Antipsychotic-induced weight gain and therapeutic response: a differential association. J Clin Psychopharmacol 2002;22:244-51.
50. Nasrallah H. A review of the effect of atypical antipsychotics on weight. Psychoneuroendocrinology 2003;28(Suppl. 1):83-96.
51. Ruiz P, Varner RV, Small DR. Ethnic differences in the neuroleptic treatment of schizophrenia. Psychiatr Q 1999;70:163-72.
52. Collazo Y, Tam R, Sramek J. Neuroleptic dosing in Hispanic and Asian Inpatients with schizophrenia. Mt Sinai J Med 1996; 63:310-3.
53. Costa e Silva JA, Álvarez N, Mazzotti G. Olanzapine as alternative therapy for patients with haloperidol-induced extrapyramidal symptoms: results of a multicenter, collaborative trial in Latin America. J Clin Psychopharmacol 2001;21:375-81.