Effectiveness of Antipsychotic Treatments for Schizophrenia: Interim 6-Month Analysis From a Prospective Observational Study (IC-SOHO) Comparing Olanzapine, Quetiapine, Risperidone, and Haloperidol

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Background: The Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study was designed to provide information regarding use and outcome of antipsychotic treatments in a large, diverse population in real practice settings.

Method: Outpatients with schizophrenia (ICD-10 or DSM-IV) who initiated or changed to a new antipsychotic entered this 3-year, naturalistic, prospective observational study. Four monotherapy treatment groups were defined according to the antipsychotic prescribed at baseline, namely olanzapine, risperidone, quetiapine, and haloperidol. Efficacy was assessed using the Clinical Global Impressions-Severity of Illness rating scale (CGI-S), inclusive of subscales for positive, negative, depressive, and cognitive symptoms. Tolerability was assessed by adverse event questionnaires and weight measurements. Six-month findings are described.

Results: At baseline, 5833 participants were prescribed monotherapy and the mean severity of illness was moderate to marked (CGI-S). At 6 months, olanzapine resulted in significantly greater improvements in overall, positive, negative, depressive, and cognitive symptoms compared with quetiapine, risperidone or haloperidol ($p < .001$). Improvements in overall, negative, and cognitive symptoms were significantly higher for risperidone compared with haloperidol ($p < .001$), whereas improvements across all symptoms were comparable for quetiapine and haloperidol. Extrapyramidal symptoms and tardive dyskinesia decreased compared with baseline in the olanzapine, quetiapine, and risperidone groups but increased in the haloperidol group ($p < .001$, likelihood of extrapyramidal symptoms with haloperidol compared with olanzapine, quetiapine, or risperidone). Sexual function adverse events were most prominent in the haloperidol and risperidone treatment groups. Weight change was significantly greater for olanzapine compared with the other antipsychotics ($p < .001$).

Conclusion: Our results support the previously reported positive impact of atypical antipsychotics, particularly olanzapine, in patients with schizophrenia.

(J Clin Psychiatry 2004;65:312–321)

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This study was supported by a research grant from Eli Lilly and Company, Indianapolis, Ind.

Drs. Dossenbach and Bitter and Mr. Hodge are employees of Eli Lilly and Dr. O'Halloran and Mr. Boland are former employees of Eli Lilly.

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Clinical practice guidelines consistently emphasize antipsychotic therapy as the keystone for management of schizophrenia.[1] Until recently, typical antipsychotics, most commonly haloperidol, were the foremost antipsychotic therapy used in both the acute and maintenance phases of this disease. Over the past decade, there has been a shift toward the use of atypical antipsychotics. Indeed, atypical agents are now used as first-line therapy for the treatment of schizophrenia and other psychotic states.[2–4] Currently, olanzapine, quetiapine, and risperidone are the most commonly prescribed atypical medications.

The literature predominantly suggests that atypical antipsychotics have a broader spectrum of clinical efficacy and are better tolerated than their typical counterparts.[5–7] Importantly, atypical agents have demonstrated that antipsychotic efficacy benefits can be achieved without considerable risk of extrapyramidal symptoms (EPS) and movement disorders,[8,9] which remain a major concern for long-term treatment with typical antipsychotics. However, recent meta-analyses propose that the findings

of a superior safety profile for atypical agents may be biased, as high-potency typical compounds were often used as the comparator typical, and that optimum doses of low-potency typical antipsychotics might not induce EPS more than do atypical medications.[10,11]

There are few publications addressing multiple comparisons between atypical antipsychotics, with the majority of published data on atypical antipsychotics reporting results from randomized controlled trials (RCTs). Controlled trials are essential for establishing the efficacy and safety of new medications. By design, however, RCTs require select populations, often excluding patients with comorbidities and substance abuse; are relatively short; and usually are not community based.[12] This restricted external validity of RCTs may present limitations when translating the findings from RCTs to real clinical practice settings, as they have indirect applicability to the general population of patients with schizophrenia.[13,14] In addition, translating RCT results to patient populations in other parts of the world might be complicated by cross-cultural or cross-ethnic variations in responses to antipsychotic agents.[15]

Ideally, the results of RCTs should be complemented by observational studies like the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study, because observational studies evaluate the effectiveness of treatments as used in real-world clinical practice settings.[16,17] The advantages of observational studies include the possibility of evaluating larger numbers of patients over longer periods of time, in realistic clinical situations, and with minimal inclusion or exclusion criteria. However, to date, most observational studies of antipsychotics have been insufficient in size and duration and have been retrospective in design. Retrospective studies, by their nature, are designed after data are collected and thus provide less rigorous conclusions. Prospective observational studies, therefore, provide the strongest observational data to complement RCT findings. Such studies are needed in the area of antipsychotic treatment and are increasing in frequency.[18–21]

The IC-SOHO study is an ongoing prospective, observational study designed to evaluate a large and diverse population across 4 continents over 3 years. A parallel SOHO study has also commenced in Europe (EU-SOHO)[20] and Brazil, results from which will ultimately provide the current study with a wider perspective. The SOHO studies use a wide range of simple but valid measures that examine the impact of antipsychotics in the treatment of schizophrenia. This article describes the results from the first 6 months of IC-SOHO across the entire intercontinental sample. We compare the effectiveness of olanzapine, quetiapine, risperidone, and haloperidol as antipsychotic treatments for schizophrenia, with a specific focus on the atypical antipsychotic olanzapine.

METHOD

Study Design

The IC-SOHO study (study code: F1D-SN-HGJR) is a 3-year, global, prospective, observational study of antipsychotic medications used for the treatment of schizophrenia. This study is naturalistic and is designed to assess clinical, functional, quality of life, and economic outcomes that reflect real life settings. This study is also open-label; medications include any available and registered antipsychotic treatments for schizophrenia (these may have differed between countries).

Participating Countries

This article includes data from 27 countries in Africa, Asia, Central and Eastern Europe, Latin America, and the Middle East. These countries are Algeria, Argentina, Chile, Colombia, Costa Rica, Czech Republic, Egypt, El Salvador, Guatemala, Honduras, Hungary, Israel, Korea, Lithuania, Malaysia, Mexico, Peru, Poland, Puerto Rico, Romania, Russia, Saudi Arabia, Slovakia, Slovenia, Taiwan, Turkey, and Venezuela.

Inclusion Criteria

At their discretion, participating psychiatrists who were trained with study procedures offered entry to patients with a clinical diagnosis of schizophrenia (ICD-10 or DSM-IV) who met the following entry criteria: (1) initiated or changed antipsychotic medication for the treatment of schizophrenia, (2) presented with the normal course of care in an outpatient setting or in hospital when admission was planned for the initiation or change of antipsychotic medication with discharge planned within 2 weeks, (3) at least 18 years of age, and (4) not simultaneously participating in an interventional study.

Patient Consent

To enable the release of their personal information, patients (or their legal representative) were required to provide at least oral consent; 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.

Treatment Arms

This study did not follow randomized treatment-group assignment because it has a naturalistic, observational design. Each participating psychiatrist was asked to enter patients by using an alternating structure of entry between 2 treatment arms until a block of 10 was achieved (i.e., 5 in each group). The 2 treatment arms were (1) patients who were initiated or changed to olanzapine as their antipsychotic therapy and (2) patients who were initiated or

changed to any other alternative antipsychotic agent. To ensure that the study reflects the naturalistic setting within each country, psychiatrists were instructed first to make treatment decisions independent of the study using their standard clinical practice guidelines and then evaluate whether patients were eligible for participation on the basis of the inclusion criteria and the alternating structure of entry. Choice of antipsychotic and dose prescribed was at the psychiatrist's discretion.

Treatment Groupings

To facilitate comparisons of outcomes associated with individual antipsychotics, post hoc treatment groups were established. Accordingly, the 2 treatment arms were regrouped by the antipsychotic initiated or changed to at baseline. To establish a homogenous sample and to enable attribution of results to individual antipsychotics, patients taking a combination of antipsychotics were excluded from this post hoc analysis. Comparisons were made between 4 monotherapy treatments: olanzapine (N = 3222), quetiapine (N = 189), risperidone (N = 1116), and haloperidol (N = 256). Clozapine was excluded from this analysis as this drug is recommended for and limited to treatment-resistant schizophrenia. Small sample size for the newer atypicals amisulpride (N = 34), ziprasidone (N = 28), and zotepine (N = 42) precluded their inclusion. The only typical antipsychotic included in this analysis was haloperidol (N = 256), as other typicals were not prescribed as frequently as haloperidol (flupenthixol [N = 116] and zuclopenthixol [N = 106] were the next most commonly prescribed typicals). Treatment groups were established on the basis of the intention-to-treat principle, meaning patients were included in the treatment group to which they were assigned even if the patient did not adhere to this treatment throughout the remainder of the study.

For certain additional analyses of patients who remained on monotherapy, the haloperidol and risperidone treatment groups were subdivided into 2 dose groups on the basis of the modal dose from baseline to 6 months. For haloperidol, the 2 dose groups were ≤ 12 mg/day (N = 84; mean [SD] modal dose = 6.1 [3.00] mg/day) and > 12 mg/day (N = 37; mean [SD] modal dose = 22.9 [7.4] mg/day). For risperidone, the 2 dose groups were < 6 mg/day (N = 507; mean [SD] modal dose = 3.0 [1.1] mg/day) and ≥ 6 mg/day (N = 184; mean [SD] modal dose = 6.5 [1.2] mg/day).

Outcome Measures

The clinical status of patients was measured using the Clinical Global Impressions-Severity of Illness rating scale (CGI-S).[22] The CGI-S was adapted[23] to include an additional 4 symptom domains (positive, negative, depressive, and cognitive symptoms), each rated from 1 to 7 (1 = normal, 7 = severely ill). Responders were defined as those having an overall baseline CGI-S score of ≥ 4, which subsequently decreased by ≥ 2, or an overall baseline CGI-S score of 3, which subsequently decreased by ≥ 1; therefore, by definition, patients that had an overall CGI-S score of 1 or 2 at baseline were excluded from this analysis. Patient baseline demographics, treatment patterns throughout the study, prescription of concomitant medications, and treatment tolerability as assessed by adverse event questionnaires and weight measurements were also recorded.

Analysis

Data were collected for this interim analysis at baseline, 3 months, and 6 months. Statistical analyses were performed using SAS version 8.2 for Windows (SAS Institute, Cary, N.C.). Continuous variables were described using summary statistics such as means and standard deviations. Categorical variables were described using frequencies and percentages. Patients with missing data were excluded from relevant analyses. Differences across the olanzapine, quetiapine, risperidone, and haloperidol treatment groups (as monotherapy only) were tested using analysis of variance (continuous variables) or logistic regression (categorical variables).

To adjust for baseline differences of postbaseline data, the following variables were used as covariates in the analysis of variance and logistic regression models: age, duration of diagnosis, gender, overall baseline CGI-S scores, prior use of depot typicals, prior use of clozapine, and hospitalization in the 6 months prior to baseline. For analysis of continuous changes from baseline, the baseline value of the variable was also included as a covariate in the analysis of variance model. Where the difference across the treatment groups was significant, further pairwise comparisons between treatment groups were performed using contrasts.

Given the large number of statistical comparisons undertaken in this analysis of the IC-SOHO data, the level required for statistical significance was defined a priori to be $p \leq .001$.

RESULTS

Baseline Demographics

Of the total 7658 patients participating in the IC-SOHO study, 76% (N = 5833) were initiated or changed to monotherapy upon entry. Table 1 describes the baseline characteristics of the overall patient population prescribed monotherapy and specifically of those patients prescribed olanzapine, quetiapine, risperidone, or haloperidol (as monotherapy) upon entry.

Treatment Patterns

The median dose of olanzapine and haloperidol remained at 10.0 mg/day throughout the 6 months (Table 2).

Table 1. Baseline Characteristics of Patients With Schizophrenia Prescribed Monotherapy Antipsychotics at Study Entry[a]

Characteristic	Overall[b] (N = 5833)	Olanzapine (N = 3222)	Quetiapine (N = 189)	Risperidone (N = 1116)	Haloperidol (N = 256)
Percentage of total population (N = 7658)	76	42	2	15	3
Percentage of monotherapy population (N = 5833)	100	55	3	19	4
Gender					
Women, % (N)	46 (2666)	45 (1438)	50 (93)	49 (541)	47 (121)
Age, mean (SD), y	35.5 (12.2)	34.9 (12.1)	34.4 (12.0)	35.9 (12.2)	35.0 (11.5)
Duration of illness, mean (SD), y	9.1 (9.9)	8.5 (9.7)	9.0 (10.1)	9.0 (10.0)	9.5 (9.8)
Neuroleptic naive, % (N)	16 (921)	18 (565)	10 (19)	18 (193)	18 (44)
Clinical status,[c] mean (SD), score					
Overall symptoms	4.33 (1.06)	4.36 (1.07)	4.35 (1.07)	4.23 (1.04)	4.37 (1.07)
Positive symptoms	3.92 (1.40)	3.92 (1.41)	3.89 (1.49)	3.88 (1.38)	4.24 (1.36)
Negative symptoms	3.93 (1.32)	3.96 (1.33)	4.07 (1.37)	3.83 (1.26)	3.76 (1.36)
Depressive symptoms	3.26 (1.39)	3.33 (1.40)*	3.48 (1.43)*	3.24 (1.33)*	2.90 (1.39)
Cognitive symptoms	3.67 (1.36)	3.69 (1.37)	3.62 (1.33)	3.58 (1.34)	3.61 (1.37)

[a]Acutal numbers of patients contributing to percentage calculations may differ from the number of patients in each treatment group due to missing data and patients not remaining on originally prescribed drug.
[b]All monotherapy patients only.
[c]According to the Clinical Global Impressions-Severity of Illness rating scale (1 = normal to 7 = extremely ill).
*Significantly ($p \leq .001$) different compared with haloperidol.

Table 2. Dose of Olanzapine (N = 3222), Quetiapine (N = 189), Risperidone (N = 1116), and Haloperidol (N = 256) Prescribed at Each Visit[a]

	Dose, mg			
Timepoint	Olanzapine	Quetiapine	Risperidone	Haloperidol
Baseline				
Mean (SD)	9.7 (4.0)	241.1 (165.4)	3.4 (1.7)	12.0 (9.3)
Median	10.0	200.0	3.0	10.0
Mode	10.0	200.0	2.0	10.0
3 Months				
Mean (SD)	10.8 (4.6)	338.2 (204.0)	3.9 (1.9)	11.5 (8.8)
Median	10.0	300.0	4.0	10.0
Mode	10.0	400.0	4.0	10.0
6 Months				
Mean (SD)	10.9 (4.8)	339.5 (188.9)	4.0 (2.1)	12.2 (9.3)
Median	10.0	300.0	4.0	10.0
Mode	10.0	200, 400[b]	4.0	10.0

[a]Actual numbers of patients contributing to dose calculations may differ from the number of patients in each treatment group due to missing data and patients not remaining on originally prescribed drug.
[b]Two modes.

The median dose of quetiapine increased from 200.0 mg/day at baseline to 300.0 mg/day at 3 and 6 months. The median dose of risperidone increased during treatment from 3.0 mg/day at baseline to 4.0 mg/day at 3 months and remained at 4.0 mg/day at 6 months.

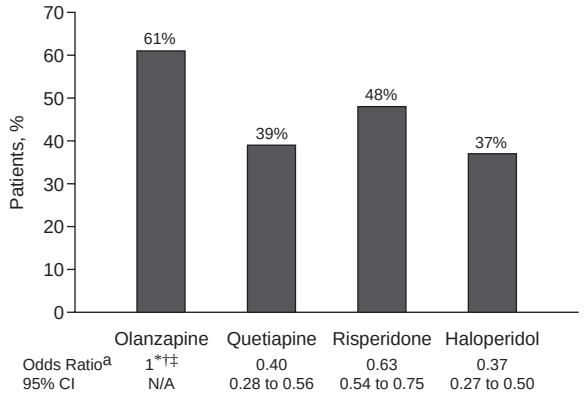
Changes to prescription patterns within each treatment group were determined during the first 6 months for patients with relevant data available. Two major categories were considered: patients who remained on the same drug as monotherapy and patients who changed drugs. The group of patients who remained on the same drug was further divided on the basis of dosage information into patients who remained on the drug at a constant dose and patients who remained on the drug with a changing dose (including decreasing, increasing, and varying dose). As a result of missing data, the number of patients in each subgroup may differ for each comparison. Statistical comparisons for those who remained on a drug versus those who changed drugs show that the odds for remaining on the same drug were significantly higher for olanzapine (88% [2318/2631] remained on drug) compared with quetiapine (71% [110/154]), risperidone (80% [703/878]), or haloperidol (66% [134/203]) and significantly higher for risperidone compared with haloperidol ($p < .001$). Comparisons for patients who remained on the drug at a constant dose versus those who remained on the drug with a changing dose showed that the likelihood of remaining on a drug at a constant dose was significantly better for olanzapine (72% [1602/2235]) compared with quetiapine (53% [57/108]) and risperidone (60% [423/700]) ($p < .001$), with no significant difference for olanzapine compared with haloperidol (71% [84/118]).

Efficacy

Following 6 months of treatment, there was a greater proportion of responders in the olanzapine group (61%) compared with the quetiapine (39%), risperidone (48%), or haloperidol (37%) treatment groups ($p < .001$; odds ratio comparisons) (Figure 1).

At 3 months, patients in the olanzapine treatment group had significantly greater improvements across all symptom domains compared with patients in the quetiapine or risperidone groups ($p < .001$) (Table 3). Olanzapine patients also showed significantly greater improvements in all symptom domains, with the exception of positive symptoms, when compared with haloperidol ($p < .001$). Patients in the risperidone treatment group had a significantly greater improvement in overall and positive symptoms compared with those in the quetiapine group ($p < .001$), and risperidone patients also improved significantly more compared with haloperidol patients for negative and cognitive symptoms ($p < .001$).

Figure 1. Proportion of Responders to Olanzapine, Quetiapine, Risperidone, and Haloperidol Treatments After 6 Months



[a]Compared with olanzapine, following baseline adjustment.
*p ≤ .001 vs. quetiapine.
†p ≤ .001 vs. risperidone.
‡p ≤ .001 vs. haloperidol.
Abbreviations: CI = confidence interval, N/A = not applicable.

Table 3. Clinical Status of Patients Following 3 and 6 Months of Antipsychotic Treatment[a]

	Summary of Scores				Change From Baseline (adjusted for baseline values)			
	3 Months		6 Months		3 Months		6 Months	
Symptom Domain	Mean	SD	Mean	SD	Mean	SEM	Mean	SEM
Overall								
Olanzapine	3.16	1.09	2.79	1.12	–1.08*†‡	0.04	–1.44*†‡	0.04
Quetiapine	3.66	1.16	3.20	1.24	–0.58†	0.08	–1.02	0.09
Risperidone	3.28	1.03	2.96	1.07	–0.90*	0.05	–1.24‡	0.05
Haloperidol	3.54	0.97	3.39	1.08	–0.68	0.07	–0.87†	0.08
Positive								
Olanzapine	2.69	1.24	2.35	1.20	–1.13*†	0.04	–1.44*†‡	0.05
Quetiapine	3.15	1.40	2.75	1.35	–0.64†	0.09	–1.01	0.10
Risperidone	2.83	1.20	2.52	1.21	–0.96*	0.05	–1.27	0.06
Haloperidol	2.96	1.20	2.84	1.23	–0.97	0.08	–1.07	0.09
Negative								
Olanzapine	3.01	1.21	2.67	1.18	–0.96*†‡	0.04	–1.21*†‡	0.04
Quetiapine	3.47	1.33	3.08	1.28	–0.55	0. 08	–0.82	0.09
Risperidone	3.18	1.16	2.87	1.12	–0.73‡	0.05	–0.98‡	0.05
Haloperidol	3.38	1.17	3.16	1.15	–0.47†	0.08	–0.65†	0.08
Depressive								
Olanzapine	2.52	1.19	2.25	1.16	–0.82*†‡	0.04	–1.11*†‡	0.04
Quetiapine	2.99	1.10	2.57	1.12	–0.40	0.08	–0.83	0.09
Risperidone	2.67	1.19	2.43	1.17	–0.62	0.05	–0.91	0.05
Haloperidol	2.65	1.23	2.58	1.28	–0.49	0.08	–0.67	0.08
Cognitive								
Olanzapine	2.82	1.22	2.52	1.17	–0.80*†‡	0.04	–1.05*†‡	0.04
Quetiapine	3.16	1.22	2.91	1.26	–0.43	0.08	–0.61	0.09
Risperidone	2.96	1.18	2.72	1.17	–0.62‡	0.05	–0.83‡	0.05
Haloperidol	3.24	1.28	3.04	1.26	–0.36†	0.07	–0.54†	0.08

[a]According to the Clinical Global Impressions-Severity of Illness rating scale (1 = normal to 7 = extremely ill).
*p ≤ .001 vs. quetiapine.
†p ≤ .001 vs. risperidone.
‡p ≤ .001 vs. haloperidol.
Abbreviation: SEM = standard error of the mean.

At 6 months, olanzapine patients continued to show significant improvements across all symptom domains when compared with quetiapine, risperidone, or haloperidol ($p < .001$). Overall, negative, and cognitive symptoms improved significantly for patients in the risperidone group compared with those in the haloperidol group ($p < .001$), but risperidone was no longer significantly different compared with quetiapine for any measure. No significant differences were noted between patients in the quetiapine and haloperidol treatment groups.

Differences were observed for change in overall symptom severity from baseline to 6 months when treatment groupings were further divided into patients remaining on their originally prescribed drug as monotherapy and patients remaining on their original drug at a constant dose (Table 4). The magnitude of change in overall symptom severity at the 6-month endpoint increased when patients who deviated from their initial prescription were removed from each treatment group; this change was further increased when patients with altered doses of their original drug were also removed. Olanzapine remained significantly superior to risperidone or haloperidol and risperidone remained significantly superior to haloperidol when patients who made a change to their baseline prescription were removed ($p < .001$). The mean change in overall symptom severity with quetiapine treatment increased closer to that reported for olanzapine when patients in both treatment groups remained on their original prescription at a constant dose; however, the standard error of the mean (SEM) change for quetiapine is comparatively large (0.13) due to the small number of patients in this group ($N = 57$).

For patients remaining on monotherapy, overall mean CGI-S score change from baseline to 6 months was not significantly different for comparisons between both haloperidol dose groups (≤ 12 mg/day: –1.02 [SEM = 0.12], > 12 mg/day: –0.61 [SEM = 0.17]).

Tolerability

Adverse events related to motor function. During the 6-month treatment period, the presence of EPS and tardive dyskinesia decreased from baseline levels in the olanzapine, quetiapine, and risperidone treatment groups but increased in the haloperidol treatment group (Table 5). At 6 months, EPS were significantly more likely to occur in patients in the haloperidol group compared with patients in the olanzapine, quetiapine, or risperidone treatment groups ($p < .001$). Furthermore, the likelihood of EPS occurring in the risperidone treatment group was significantly higher compared with the likelihood of EPS in the olanzapine or quetiapine groups ($p < .001$).

When patients who remained on monotherapy were considered, EPS were significantly more likely to occur with haloperidol treatment compared with the 3 atypicals irrespective of the haloperidol dose group (≤ 12 mg/day,

Table 4. Overall CGI-S Score at Baseline and Change at 6 Months for All Patients, Patients Remaining on Original Monotherapy Drug, and Patients Remaining on Original Drug at Constant Dose

	Baseline		Change[a]	
Treatment Group	Mean	SD	Mean	SEM
All patients on monotherapy				
Olanzapine	4.36	1.07	–1.44*†‡	0.04
Quetiapine	4.35	1.07	–1.02	0.09
Risperidone	4.23	1.04	–1.24‡	0.05
Haloperidol	4.37	1.07	–0.87†	0.08
Patients remaining on original drug as monotherapy				
Olanzapine	4.35	1.07	–1.54*†‡	0.05
Quetiapine	4.29	1.11	–1.19	0.10
Risperidone	4.22	1.07	–1.35‡	0.06
Haloperidol	4.30	1.07	–0.91†	0.10
Patients remaining on original drug at constant dose				
Olanzapine	4.33	1.07	–1.59†‡	0.05
Quetiapine	4.33	1.07	–1.29	0.13
Risperidone	4.17	1.05	–1.39‡	0.07
Haloperidol	4.22	1.13	–0.92†	0.12

[a]Change from baseline to 6 months, adjusted for baseline values.
*p ≤ .001 vs. quetiapine.
†p ≤ .001 vs. risperidone.
‡p ≤ .001 vs. haloperidol.
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness rating scale, SEM = standard error of the mean.

Table 5. Presence of Adverse Events Associated With Olanzapine (N = 3222), Quetiapine (N = 189), Risperidone (N = 1116), or Haloperidol (N = 256) at Baseline and at 6 Months[a]

	Baseline[b]		6 Months			
Adverse Event	%	N	%	N	OR[c]	95% CI
Extrapyramidal symptoms						
Olanzapine	38	1202	9	240	1†‡	N/A
Quetiapine	34	64	8	13	0.93†‡	0.52 to 1.67
Risperidone	38	410	26	232	3.64*‡	2.97 to 4.46
Haloperidol	31	76	49	105	10.01*†	7.39 to 13.56
Tardive dyskinesia						
Olanzapine	7	233	3	79	1†‡	N/A
Quetiapine	7	13	3	4	0.84	0.30 to 2.35
Risperidone	8	83	6	52	2.06	1.42 to 2.97
Haloperidol	6	14	8	17	2.90	1.65 to 5.08
Loss of libido						
Olanzapine	45	1262	28	720	1†‡	N/A
Quetiapine	51	88	30	44	1.14	0.79 to 1.66
Risperidone	44	417	41	354	1.81	1.53 to 2.13
Haloperidol	46	96	48	97	2.35	1.75 to 3.16
Impotence/sexual dysfunction						
Olanzapine	32	796	19	423	1†‡	N/A
Quetiapine	40	62	18	23	0.99	0.62 to 1.59
Risperidone	30	253	27	202	1.62	1.33 to 1.97
Haloperidol	30	57	32	54	1.97	1.39 to 2.79
Amenorrhea/menstrual disturbances[d]						
Olanzapine	33	366	17	171	1†‡	N/A
Quetiapine	45	35	13	8	0.74	0.35 to 1.59
Risperidone	31	128	28	102	1.91	1.44 to 2.54
Haloperidol	32	28	38	30	2.92	1.79 to 4.75

[a]Acutal numbers of patients contributing to percentage calculations may differ from the number of patients in each treatment group due to missing data and patients not remaining on originally prescribed drug.
[b]No significant differences were detected at baseline.
[c]Compared with olanzapine, adjusted for baseline values.
[d]Female patients aged ≤ 55 years only.
*p ≤ .001 vs. quetiapine.
†p ≤ .001 vs. risperidone.
‡p ≤ .001 vs. haloperidol.
Abbreviations: CI = confidence interval, N/A = not applicable, OR = odds ratio.

46% EPS; > 12 mg/day, 59% EPS). Also, the likelihood of EPS occurring in the risperidone treatment group was significantly higher compared with olanzapine or quetiapine ($p < .001$) irrespective of risperidone dose group (< 6 mg/day, 20% EPS; ≥ 6 mg/day, 36% EPS). Risperidone had a significant advantage over haloperidol for comparisons with the < 6-mg/day dose group only; there was no significant difference for the likelihood of EPS between haloperidol and risperidone ≥ 6 mg/day.

A greater proportion of patients in the haloperidol or risperidone treatment groups had tardive dyskinesia compared with patients in the olanzapine or quetiapine groups at 6 months. However, significant differences for the likelihood of occurrence of tardive dyskinesia were only evident for comparisons of olanzapine with risperidone or haloperidol ($p < .001$), not for comparisons of quetiapine with risperidone or haloperidol. Treatment-emergent tardive dyskinesia was observed in each treatment group (olanzapine, 1%; quetiapine, 2%; risperidone, 3%; haloperidol, 7%), again significantly different for comparisons of olanzapine with risperidone or haloperidol ($p < .001$). The lack of power due to small patient numbers in the quetiapine group should be taken into account.

Adverse events related to sexual function and hyperprolactinemia. Adverse events associated with sexual function and prolactin elevation were present at baseline, with no significant difference between groups (Table 5). At 6 months, the odds of loss of libido and impotence/sexual dysfunction were significantly less in the olanzapine compared with the risperidone or haloperidol treatment groups ($p < .001$), and comparable with quetiapine. Similarly, the likelihood that female patients in the olanzapine group would experience amenorrhea was significantly lower compared with that for risperidone or haloperidol ($p < .001$) and comparable to that of quetiapine.

Weight change. At 6 months, patients who were underweight (body mass index [BMI] < 18.5 kg/m^2) in general at baseline gained more weight compared with patients who were normal weight (BMI ≥ 18.5 to < 25 kg/m^2), overweight (BMI ≥ 25 to < 30 kg/m^2), or obese (BMI ≥ 30 kg/m^2) at baseline; this was true for each treatment group. Patients in the olanzapine group gained significantly more weight (mean = 2.57 kg [5.67 lb], SEM = 0.21 kg [0.46 lb]) compared with patients in the quetiapine (0.58 kg [1.28 lb], SEM = 0.44 [0.97 lb]), risperidone (1.49 kg [3.28 lb], SEM = 0.26 [0.57 lb]), or haloperidol (0.73 kg [1.61 lb], SEM = 0.40 [0.88 lb]) treatment groups ($p < .001$).

Table 6. Concomitant Medications Prescribed at Baseline and at 6 Months to Patients Taking Olanzapine (N = 3222), Quetiapine (N = 189), Risperidone (N = 1116), or Haloperidol (N = 256)

Concomitant Medication	Baseline[a] %	Baseline[a] N	6 Months[a] %	6 Months[a] N	OR[b]	95% CI
At least 1 concomitant medication						
Olanzapine	51†‡	1633	44	1202	1†‡	N/A
Quetiapine	53†‡	100	51	82	1.36‡	0.99 to 1.88
Risperidone	67*‡	752	60	555	1.99‡	1.71 to 2.32
Haloperidol	82*†	210	76	166	3.97*†	2.88 to 5.47
Anticholinergics						
Olanzapine	12†‡	398	9	258	1†‡	N/A
Quetiapine	11†‡	21	9	14	0.94†‡	0.54 to 1.66
Risperidone	30*‡	340	30	273	4.16*‡	3.43 to 5.05
Haloperidol	62*†	158	55	120	11.81*†	8.77 to 15.92
Antidepressants						
Olanzapine	15	474	16	426	1	N/A
Quetiapine	23	44	27	43	1.95	1.35 to 2.81
Risperidone	17	189	17	159	1.14	0.93 to 1.40
Haloperidol	11	29	18	39	1.20	0.83 to 1.73
Anxiolytics/hypnotics						
Olanzapine	32‡	1044	26	721	1†‡	N/A
Quetiapine	32	60	31	50	1.30	0.91 to 1.85
Risperidone	37	416	32	297	1.33	1.13 to 1.57
Haloperidol	46	119	43	93	2.04	1.53 to 2.72
Mood stabilizers						
Olanzapine	9	287	10	261	1	N/A
Quetiapine	7	14	7	12	0.77	0.42 to 1.42
Risperidone	9	104	9	83	0.98	0.75 to 1.27
Haloperidol	10	26	13	28	1.32	0.86 to 2.00

[a]Patients may not be taking the originally prescribed drug at 6 months.
[b]Compared with olanzapine, adjusted for baseline values.
*$p \leq .001$ vs. quetiapine.
†$p \leq .001$ vs. risperidone.
‡$p \leq .001$ vs. haloperidol.
Abbreviations: CI = confidence interval, N/A = not applicable, OR = odds ratio.

Concomitant Medications

Overall, prescription of concomitant medications decreased from baseline in all patient groups during the first 6 months of treatment (Table 6). At 6 months, patients in the olanzapine group were significantly less likely to be prescribed concomitant medications compared with risperidone or haloperidol patients ($p < .001$). Patients in the quetiapine group were significantly less likely to be prescribed concomitant medications compared with haloperidol patients ($p < .001$). The likelihood of anticholinergic prescriptions to patients in the haloperidol or risperidone groups at 6 months was significantly higher compared with that of olanzapine or quetiapine ($p < .001$). Furthermore, haloperidol patients were more likely to be prescribed anticholinergics compared with risperidone patients ($p < .001$). The odds of anxiolytics/hypnotics prescription to patients in the olanzapine group were significantly less compared with that in the haloperidol and the risperidone groups ($p < .001$). There were no significant differences for comparisons of prescription of antidepressants or mood stabilizers between groups at 6 months.

DISCUSSION

To our knowledge, this is the first analysis from a prospective observational study that directly compares the effectiveness of haloperidol, olanzapine, risperidone, and quetiapine as antipsychotic treatments for schizophrenia in a naturalistic setting. The results demonstrate that atypical antipsychotics, in particular olanzapine, are more effective and better tolerated than the typical antipsychotic haloperidol. Significant benefits were observed with olanzapine for all efficacy measures when compared with the atypicals quetiapine and risperidone. Moreover, when patients remained on their originally prescribed monotherapy drug at the initially prescribed dose, differences in efficacy remained consistent with our primary findings. Additionally, the likelihood of EPS occurring with olanzapine treatment was significantly less compared with that with risperidone or haloperidol and comparable to that observed with quetiapine treatment.

Acknowledging the limitations and inherent difficulties of observational studies, such as lack of randomization and lack of measurements that can be regarded as intervention, the IC-SOHO study endeavored to maximize internal validity through its design, comprehensiveness, large sample size, and duration. External validity was achieved by minimizing restrictive selection criteria and treatment intervention. The international nature of IC-SOHO enabled the inclusion of a wide variety of patients from different backgrounds, countries, geographies, and social statuses, thereby contributing to the knowledge of this disease in areas where information is limited. Furthermore, the outcome measures were selected on the basis of simplicity and ease of use, thereby not interfering with clinical practice under normal circumstances.

Efficacy

Our findings support previous data that consistently show olanzapine as superior to haloperidol for treatment of overall symptoms of schizophrenia[24,25] and, in particular, the positive[24] and negative[25–27] symptoms of this disease. Our data clearly emphasize the lack of effectiveness of haloperidol in treating negative, depressive, and cognitive symptoms, all of which may coexist with positive symptoms and can become more apparent when positive symptoms are under control.[28–30]

A recent metaregression analysis[11] identified a significant advantage for atypical antipsychotics as the dose of haloperidol increased to > 12 mg/day. However, this observed advantage in favor of the atypical antipsychotics disappeared as the dose of haloperidol decreased to ≤ 12 mg/day.[11] In our study, we found that overall symptom improvements were not significantly different for comparisons between both haloperidol dose groups.

In our study, olanzapine patients experienced significantly greater clinical improvements across all symptom

domains compared with risperidone and quetiapine. A number of studies have demonstrated greater efficacy of olanzapine over risperidone at reducing symptom severity, including various symptom domains.[29,31–33] However, other studies have shown no difference between these agents for a number of efficacy measures, and some studies have shown greater clinical improvements with risperidone.[34,35] The reason for these differences is unclear. Possibly, the dose of risperidone used in some instances may not have been sufficient to achieve maximal benefits. In our study, the mean dose of risperidone remained at ≤ 4 mg/day during the 6 months. Whereas other studies have recommended somewhat higher doses (4 to 6 mg/day), Sacristan et al.[36] found that doses of risperidone higher than 6 mg/day were generally prescribed if, at baseline, patients had a mean overall CGI-S score of > 5.

Most studies published on quetiapine compare it with either placebo or typical antipsychotics, specifically haloperidol. To our knowledge, this is the first analysis from an observational study to directly compare quetiapine with olanzapine or risperidone. We found olanzapine was significantly superior to quetiapine on all measures of efficacy; although we did observe that when patients in both treatment groups remained on their initial prescription at a constant dose, the improvement in overall symptoms remained numerically superior for olanzapine but was no longer significantly different from quetiapine. These results are somewhat inconclusive due to the relatively low number of patients remaining in the quetiapine group at that point. Moreover, we found that the likelihood that patients in the olanzapine group would remain on their initially prescribed drug at a constant dose was significantly greater compared with the likelihood in the quetiapine group.

The mean dose of quetiapine recorded in this study was at the lower end of the dose range recommended for this drug. It is worth noting that, in this study, the dose of antipsychotic prescribed was entirely at the discretion of the treating psychiatrist. Pivotal trials have shown quetiapine to be effective at controlling symptoms of schizophrenia at doses ranging from > 250 mg/day up to 750 mg/day.[37–39] However, superior efficacy of quetiapine compared with haloperidol was reported at high mean doses (600 mg/day) of quetiapine,[40] and comparable efficacy of quetiapine compared with risperidone was observed when lower mean doses (254 mg/day) of quetiapine were recorded.[41]

Overall, our observations support assertions of differential efficacy between atypical antipsychotics. A meta-analysis by Tandon and Jibson[7] comparing olanzapine, risperidone, and quetiapine suggests that these agents are essentially equivalent to one another in terms of efficacy, while others[9] agree with controlled trials[25] reporting disparities between atypicals, albeit clinically modest differences. However, despite the different conclusions reported in publications on efficacy of atypical agents, all publications concur that the side effect profiles of atypical antipsychotics differ, sometimes considerably.

Tolerability

In this study, the likelihood of EPS occurring in patients in the olanzapine or quetiapine treatment groups was significantly less compared with that of risperidone and significantly higher for patients in the haloperidol group compared with that of each atypical group. The latter finding agrees with many previous studies in which haloperidol was shown to have a strong tendency to induce EPS,[8,42] despite the fact that anticholinergics are often coprescribed significantly more frequently with haloperidol,[42] as was the case in our study. Our findings also support previous safety data that show olanzapine treatment has consistently resulted in significantly lower incidences of EPS compared with haloperidol[19,42,43] and risperidone.[31,44] Furthermore, we found no significant difference for odds of experiencing EPS between both haloperidol dose groups (≤ 12 mg/day and > 12 mg/day). Indeed, the likelihood of EPS was significantly lower within each atypical treatment group irrespective of the haloperidol dose group. These findings are contrary to suggestions[10,11] that inappropriately high doses of the comparator typical agent account for superiority of atypicals on measures of tolerability.

Of the atypical antipsychotics considered in this analysis, the likelihood of EPS was significantly greater with risperidone compared with that of olanzapine or quetiapine, despite the low mean dose of risperidone prescribed in our study. Like the other atypicals, risperidone was found to be superior to haloperidol on measures of EPS; however, there was no significant difference observed when patients remaining on monotherapy risperidone at ≥ 6 mg/day were compared with those taking haloperidol. This is in support of reports that risperidone overlaps typical antipsychotics in its dose-dependent risk of inducing EPS and probably also inducing tardive dyskinesia.[6,45,46]

Our baseline data confirm that adjunctive medications are commonly coprescribed along with antipsychotics to patients with schizophrenia. Anticholinergics made up a large part of concomitant medication prescriptions at baseline, perhaps reflective of the presence of EPS and tardive dyskinesia. As anticholinergics are more commonly coprescribed with typical or EPS-inducing antipsychotics,[36] it is not surprising that a high proportion of haloperidol-treated patients were also prescribed these medications, in agreement with previous reports.[42] However, it is noteworthy that prescription of anticholinergics decreased in the haloperidol group at 6 months and that this decrease coincided with an increase in the incidence of both EPS and tardive dyskinesia in this group. The lowest rates of anticholinergic prescriptions were observed in the olanzapine and quetiapine treatment groups, support-

ing the relatively benign EPS and tardive dyskinesia profiles reported for these agents.

Sexual function disorders have become important adverse events of antipsychotic treatment. In this study, adverse events of sexual functioning were high at baseline but decreased over time in both the olanzapine and quetiapine treatment groups. This may be a reflection of improvements in clinical status of patients; however, it is possible that both of these agents may have normalized hyperprolactinemia present at baseline,[47] although prolactin levels were not measured. Our observations also demonstrate that adverse events associated with sexual function and prolactin elevation were highest with haloperidol and, compared with the atypicals, were highest with risperidone. These results support findings that typical antipsychotics[48,49] and risperidone[49,50] consistently elevate plasma levels of prolactin and, as a probable consequence, have been observed to cause increased problems with sexual function. Prolactin elevation may occur transiently during olanzapine treatment, but the elevation does not persist nor does it exceed normal values.[5,45,51] Quetiapine does not cause elevation of plasma prolactin levels[51,52]; however, long-term data are lacking.

It is well documented that antipsychotic drugs are associated with weight gain,[1] which, for most antipsychotic drugs, is intrinsically related to their mode of action.[53] In this study, patients in the olanzapine group gained the most weight followed by those in the risperidone, haloperidol, and quetiapine groups. This distribution of weight gain by treatment group is consistent with results from other studies.[21,54] However, the magnitude of weight gain observed for each treatment in this outpatient population is lower than that reported for other studies.[55–57] This difference may be attributed to ethnic variability within the IC-SOHO sample population, as other reports include predominantly white populations.[55–57]

Conclusion

The IC-SOHO project is an exploratory observational study involving multiple analyses, and, as such, care should be taken in interpretation of the results. Unlike in randomized controlled trials, selection bias could not be accounted for and inherent differences present in treatment groups may not have been fully accommodated by the baseline corrections performed. Acknowledging these and other underlying limitations, we believe our observations confirm findings that atypical antipsychotics confer benefits not always attainable with typical antipsychotics, particularly in terms of control of symptoms and lower incidence of adverse events. On the basis of our results to date, we conclude that olanzapine was significantly more effective at improving overall, positive, negative, depressive, and cognitive symptoms of schizophrenia compared with quetiapine, risperidone, or haloperidol in this sample population. Furthermore, olanzapine was found to be significantly superior to haloperidol or risperidone and comparable to quetiapine on our principal measures of tolerability.

Drug names: clozapine (Clozaril and others), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), ziprasidone (Geodon).

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