Response and Relapse in Patients With Schizophrenia Treated With Olanzapine, Risperidone, Quetiapine, or Haloperidol: 12-Month Follow-Up of the Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) Study

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Objective: The primary aim of this study was to compare the effectiveness of 12 months' treatment with olanzapine, risperidone, quetiapine, or haloperidol in preventing relapse of schizophrenia. The study also examined other measures of clinical effectiveness and tolerability.

Method: Outpatients with schizophrenia (ICD-10 or DSM-IV), who initiated or changed antipsychotic treatment, entered this 3-year, naturalistic, prospective, observational study between November 2000 and December 2001. At baseline, subsets of patients were prescribed monotherapy with olanzapine (N = 3222), risperidone (N = 1116), quetiapine (N = 189), or haloperidol (N = 256). Patients remaining on monotherapy were assessed using the Clinical Global Impression–Schizophrenia scale. Relapse rate was determined from the responder subset. Treatment patterns, patient perception of treatment compliance, substance and alcohol intake patterns, and treatment tolerability were recorded. Results are based on 12-month treatment data.

Results: Compared to haloperidol-treated patients, olanzapine- and risperidone-treated patients had approximately 3 to 4 times higher odds of response at 12 months ($p \leq .001$) and 6 times lower odds of relapse ($p \leq .001$ for olanzapine-treated patients). Among patients treated with atypical antipsychotics, olanzapine- and risperidone-treated patients had lower odds of relapse (although the difference was not significant at $p \leq .001$) and significantly higher odds of response ($p \leq .001$) compared to quetiapine-treated patients. The tolerability profile generally favored the atypical antipsychotics over haloperidol.

Conclusion: These interim results support the findings of randomized controlled trials and verify that in this naturalistic study, patients treated with olanzapine or risperidone monotherapy were less likely to experience relapse than patients who received haloperidol. The clinical effectiveness and tolerability profile varied significantly between the atypical antipsychotics.

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Clinical relapse is a common feature of schizophrenia and is typically characterized by a worsening or recurrence of psychotic symptoms. One-year relapse rates have been shown to be as high as 42%, even in treated patients.[1] Relapse frequently results in hospitalization of affected patients and contributes substantially to psychiatric health care costs.[2] Furthermore, frequent episodes and prolonged duration of relapses may impair prognosis[3,4] and lead to reduced responsiveness to antipsychotic medication.[5] Therefore, relapse prevention is critical in the long-term management of schizophrenia.

Atypical antipsychotics have been shown to be highly effective in preventing relapse in placebo-controlled trials.[6–8] However, studies directly comparing the relative

efficacies of atypical antipsychotics are lacking.[9–11] Given the chronic nature of schizophrenia, long-term maintenance studies of treatment outcomes in routine clinical practice are needed.[11–13]

The Intercontinental Schizophrenia Outpatient Health Outcomes (IC-SOHO) study is a 3-year, prospective, observational study designed to evaluate treatment outcomes in schizophrenia patients in a large and diverse population.[14] One of the treatment outcomes measured in this study was relapse rate. To our knowledge, this is the first study to compare relapse rates between atypical and typical antipsychotics in a naturalistic, clinical practice setting. The purpose of this report was to compare the effectiveness of 12 months of monotherapy treatment with olanzapine, quetiapine, risperidone, or haloperidol in the prevention of relapse of schizophrenia.

METHOD

Study Design

The IC-SOHO study is a 3-year, global, prospective, observational study of health outcomes associated with antipsychotic medication in outpatients treated for schizophrenia (Study code: F1D-SN-HGJR). All patients were recruited into the study between November 14, 2000, and December 2001 and had completed 12 months of follow-up at the time of this report. This study is currently being conducted in 27 countries. The study methods for the IC-SOHO study have been described in detail previously[14] and are summarized here.

To ensure the study reflected real-life clinical practice, patient care was at the discretion of the participating psychiatrist. Treatments were open-label and included any available antipsychotic registered for the treatment of schizophrenia (i.e., treatments may have differed between countries). There were no randomized treatment-group assignments. Each participating psychiatrist was instructed to make treatment decisions independent of the study and then enter eligible patients using an alternating entry structure. The entry structure consisted of 2 treatment arms: (1) patients who had initiated or changed to olanzapine therapy (monotherapy or in combination with other agents) or (2) patients who had initiated or changed to non-olanzapine antipsychotic therapy. Psychiatrists entered patients into the 2 treatment arms until a block of 10 patients was achieved (i.e., 5 in each group). Choice of antipsychotic and the dose prescribed was at the discretion of the psychiatrist. Patients were permitted to use concomitant medications such as anticholinergics, antidepressants, anxiolytics, and mood stabilizers, as clinically indicated.

Patients

Patients were eligible to enter the IC-SOHO study if they (1) were diagnosed with schizophrenia (ICD-10[15] or *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition [DSM-IV][16]), (2) presented during the normal course of care, (3) initiated or changed antipsychotic therapy for the treatment of schizophrenia, (4) were at least 18 years of age, and (5) were not simultaneously participating in an interventional study.

Patients from 27 countries throughout Africa, Asia, Central and Eastern Europe, Latin America, and the Middle East participated in the study. The countries involved were Algeria, Argentina, Chile, Colombia, Costa Rica, Czech Republic, Egypt, El Salvador, Guatemala, Honduras, Hungary, Israel, Lithuania, Malaysia, Mexico, Peru, Poland, Puerto Rico, Romania, Russia, Saudi Arabia, Slovakia, Slovenia, South Korea, Taiwan, Turkey, and Venezuela.

The study was conducted in accordance with each country's local ethics and regulatory requirements. All participants provided informed consent as required by local regulations.

Outcome Measures

The clinical status of patients was measured using the Clinical Global Impression–Schizophrenia (CGI-SCH) scale[17] at baseline and 3, 6, and 12 months. The CGI-SCH scale was adapted from the Clinical Global Impressions scale to include an additional 4 symptom domains (positive, negative, depressive, and cognitive symptoms), each rated from 1 to 7 (1 is normal and 7 is severely ill). On the basis of overall CGI-SCH score, patients were classified as having responded, relapsed, worsened, or remained minimally symptomatic, as appropriate. Patients could be counted in 1 or more of these classification categories. Responders were defined as having an overall baseline CGI-SCH score of ≥ 4, which subsequently decreased by 2 or more points, or an overall baseline CGI-SCH score of 3, which subsequently decreased by 1 point or more. For the subset of responders only, relapse was defined as a reversal of the improvement in the overall CGI-SCH score back to the severity at baseline or worse and/or an increase in the overall CGI-SCH score by 2 or more points from the best (lowest) overall score recorded at previous visits. Worsening was defined as an increase in the overall CGI-SCH score, compared to the lowest score recorded at previous visits, provided the current score was > 2. Patients were defined as minimally symptomatic if their overall CGI-SCH score was 1 or 2 at follow-up visits.

Patient demographics were recorded at baseline. Treatment patterns, patient perception of treatment compliance, substance and alcohol intake patterns, and treatment tolerability were also recorded during the 12-month treatment period.

Treatment Groupings and Analyses

To facilitate comparisons of outcomes associated with individual antipsychotics, post hoc treatment groups were

Table 1. Baseline Characteristics of Patients With Schizophrenia Prescribed Antipsychotics as Monotherapy at Their Baseline Visit

Characteristic	Monotherapy (N = 5833)	Olanzapine (N = 3222)	Risperidone (N = 1116)	Quetiapine (N = 189)	Haloperidol (N = 256)
Percentage of total population (N = 7658)	76	42	15	2	3
Percentage of monotherapy population (N = 5833)	100	55	19	3	4
Women, N (%)[a]	2666 (46)	1438 (45)	541 (48)	93 (49)	121 (47)
Age, mean (SD), y	35.5 (12.2)	34.9 (12.1)	35.9 (12.2)	34.4 (12.0)	35.0 (11.5)
Duration of illness, mean (SD), y	9.1 (9.9)	8.5 (9.7)	9.0 (10.0)	9.0 (10.1)	9.5 (9.8)
Neuroleptic naive, N (%)[a]	921 (16)	565 (18)	193 (17)	19 (10)	44 (17)
CGI-SCH[b] score, mean (SD)					
Overall symptoms	4.33 (1.06)	4.36 (1.07)	4.23 (1.04)	4.35 (1.07)	4.37 (1.07)
Positive symptoms	3.92 (1.40)	3.92 (1.41)	3.88 (1.38)	3.89 (1.49)	4.24 (1.36)
Negative symptoms	3.93 (1.32)	3.96 (1.33)	3.83 (1.26)	4.07 (1.37)	3.76 (1.36)
Depressive symptoms	3.26 (1.39)	3.33 (1.40)[c]	3.24 (1.33)[c]	3.48 (1.43)[c]	2.90 (1.39)
Cognitive symptoms	3.67 (1.36)	3.69 (1.37)	3.58 (1.34)	3.62 (1.33)	3.61 (1.37)

[a]Percentages were calculated using number of patients with available data.
[b]The Clinical Global Impression–Schizophrenia (CGI-SCH) scale is scored from 1 (normal) to 7 (severely ill).
[c]Significantly ($p \leq .001$) different compared with haloperidol (analysis of variance model).

established. Accordingly, the 2 treatment arms were regrouped by the antipsychotic initiated or changed to at baseline. The following monotherapy treatment groups were established: olanzapine (N = 3222), risperidone (N = 1116), quetiapine (N = 189), and haloperidol (N = 256). To enable attribution of results to individual antipsychotics, outcome measures were subsequently analyzed based on the patients who remained on the originally prescribed monotherapy; that is, patients were included in the treatment group analyses for as long as they remained on the originally prescribed monotherapy during the 12 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, resulting in differences in patient numbers for each variable. Differences across the olanzapine, quetiapine, risperidone, and haloperidol treatment groups (as monotherapy only) were tested using analysis of variance (ANOVA; continuous variables) or logistic regression (categorical variables). To adjust for baseline differences and to account for factors that may be related to clinical outcomes, the following variables were used as covariates in the ANOVA and logistic regression models for post-baseline data: age, duration of illness, gender, overall baseline CGI-SCH scores, prior use of depot typical antipsychotics, prior use of clozapine, and hospitalization in the 6 months prior to baseline. Adjusted analyses are presented as changes from baseline for continuous data (e.g., clinical status) and as changes from baseline up to 12 months for categorical data (e.g., adverse events, substance/alcohol abuse). In these analyses, the baseline value or baseline status of the variable was included as a covariate in the ANOVA or logistic regression model. When the overall test for differences across the treatment groups was significant, further pairwise comparisons between treatment groups were performed. Given the large number of statistical comparisons undertaken overall in the analyses of the IC-SOHO data, the level required for statistical significance was defined, a priori, to be $p \leq .001$.[14]

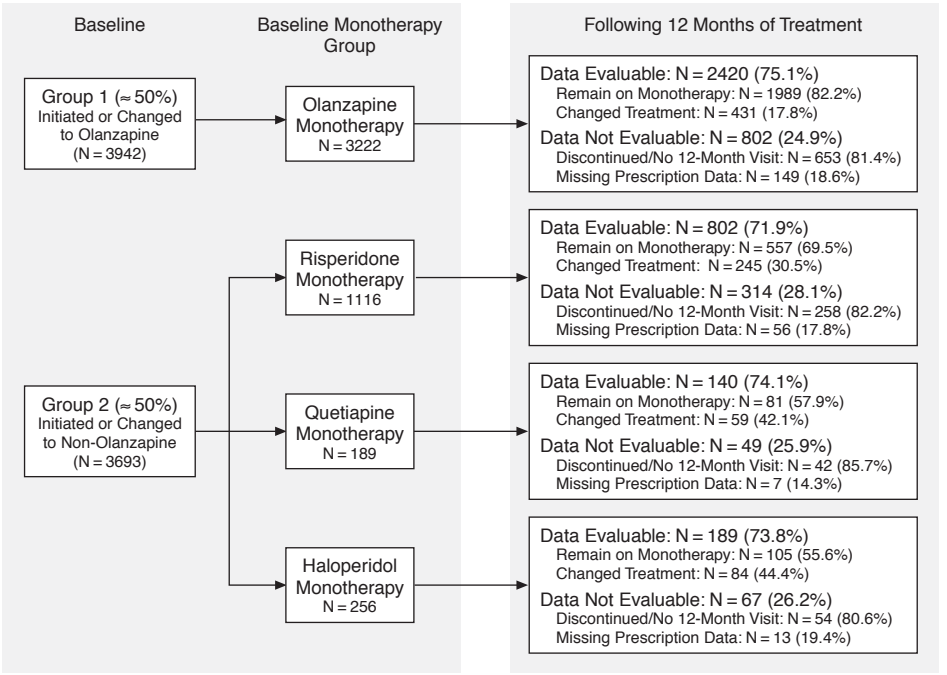
RESULTS

Patients

Of the 7658 schizophrenia patients enrolled in IC-SOHO, 76.2% (N = 5833) were prescribed monotherapy upon entry. Most of these patients were prescribed olanzapine (N = 3222), risperidone (N = 1116), quetiapine (N = 189), or haloperidol (N = 256). Generally, there were no significant differences in baseline patient characteristics between the 4 treatment groups, except for depressive symptoms (Table 1). Depressive symptoms were significantly lower among patients in the haloperidol group compared to patients in the other treatment groups.

At the end of 12 months, there were significant differences between the treatment groups in the proportion of patients who remained on monotherapy (Figure 1). Of the evaluable patients with prescription data available at 12 months, the proportion of patients who remained on the originally prescribed medication as monotherapy was 82.2% (N = 1989) for olanzapine, 69.5% (N = 557) for risperidone, 57.9% (N = 81) for quetiapine, and 55.6% (N = 105) for haloperidol. Patients on olanzapine treatment had significantly higher odds of staying on the originally prescribed medication compared to patients treated with risperidone (odds ratio [OR] = 2.04, 95% confidence interval [CI] = 1.70 to 2.45; $p \leq .001$), quetiapine (OR = 3.38, 95% CI = 2.38 to 4.82; $p \leq .001$), or haloperidol

Figure 1. Number of Patients Prescribed Baseline Monotherapy With Olanzapine, Risperidone, Quetiapine, or Haloperidol and Treatment Status Following 12 Months of Antipsychotic Monotherapy[a]



[a]Percentage calculations were based on the number of evaluable patients with non-missing prescription data for the 12-month period (olanzapine N = 2420, risperidone N = 802, haloperidol N = 189, quetiapine N = 140).

(OR = 3.59, 95% CI = 2.64 to 4.87; $p \leq .001$). Patients prescribed risperidone had significantly higher odds of staying on monotherapy compared to patients prescribed haloperidol (OR = 1.76, 95% CI = 1.27 to 2.43; $p \leq .001$).

Dosage

For patients who remained on monotherapy during the entire 12-month period, there were only slight changes in dosing patterns from the baseline to the 12-month visit. The mean doses increased slightly for all treatment groups. The mean ± SD baseline and 12-month doses were 9.9 ± 4.0 and 10.8 ± 4.8 md/day for olanzapine, 3.6 ± 1.7 and 4.0 ± 2.2 mg/day for risperidone, 251.2 ± 164.6 and 334.1 ± 199.1 mg/day for quetiapine, and 11.3 ± 9.6 and 11.8 ± 8.8 mg/day for haloperidol. The median dose of olanzapine and haloperidol remained at 10.0 mg/day throughout the 12 months. The median dose of quetiapine increased from 200.0 mg/day at baseline to 300.0 mg/day at 12 months, and the median dose of risperidone increased from 3.0 mg/day to 4.0 mg/day.

Response

The proportion of responders varied between treatment groups, both during the 12-month treatment period and at the 12-month visit. The olanzapine group had the highest proportion of patients who had responded at some time during the 12-month treatment period (81.0%, 1781/2198), followed by the risperidone (73.7%, 479/650), quetiapine (64.0%, 55/86), and haloperidol (59.3%, 73/123) treatment groups. The odds of response were significantly different between the olanzapine group and the quetiapine and haloperidol treatment groups ($p \leq .001$). The proportion of patients who responded was also significantly higher in the risperidone group compared to the haloperidol group ($p \leq .001$). The proportion of patients responding at 12 months was also highest in the olanzapine group, followed by the risperidone, quetiapine, and haloperidol treatment groups (Table 2). The odds of response were significantly higher in the olanzapine group compared to the quetiapine and haloperidol groups ($p \leq .001$) and were observed to differ from those for risperidone (but the difference did not reach the a priori level of significance; $p = .0013$). Patients treated with risperidone also had significantly higher odds of response compared to patients treated with quetiapine or haloperidol (risperidone vs. quetiapine: OR = 2.45, 95% CI = 1.44 to 4.19; $p \leq .001$; risperidone vs. haloperidol: OR = 2.90, 95% CI = 1.79 to 4.72; $p \leq .001$).

A large proportion of patients in each group were minimally symptomatic at some point during the 12-month period. The proportion of patients who were minimally symptomatic at some time during the 12-month

Table 2. Response and Relapse Rates of Patients With Schizophrenia Remaining on Treatment With Their Original Drug as Monotherapy at the 12-Month Follow-Up Visit

	Response[a]			Relapse[a,c]		
Treatment	N/Total N	%	OR[b] (95% CI) for Response	N/Total N	%	OR[b] (95% CI) for Relapse
Olanzapine	1329/1803	73.7	1[d,e] (NA)	57/1273	4.5	1[e] (NA)
Risperidone	327/513	63.7	0.70[d,e] (0.56 to 0.87)	16/302	5.3	1.06 (0.59 to 1.91)
Quetiapine	33/69	47.8	0.29 (0.17 to 0.48)	5/40	12.5	3.28 (1.17 to 9.15)
Haloperidol	36/87	41.4	0.24 (0.15 to 0.38)	6/38	15.8	5.69 (2.16 to 15.00)

[a]Patients with missing data were excluded from the analysis.
[b]ORs are for comparison with olanzapine. p Values were obtained from logistic regression models adjusted for baseline values.
[c]Only patients who had previously responded were included in the analysis.
[d]$p \leq .001$ vs. quetiapine.
[e]$p \leq .001$ vs. haloperidol.
Abbreviations: CI = confidence interval, NA = not applicable, OR = odds ratio.

Table 3. Clinical Global Impression–Schizophrenia Scale Scores[a] for Patients With Schizophrenia Remaining on Treatment With Their Original Drug as Monotherapy at the 12-Month Follow-Up Visit

	Score		Change From Baseline	
Symptom Domain	Mean	SD	Least Squares Mean	SEM
Overall symptoms				
Olanzapine	2.43	1.02	–1.80[b,c,d]	0.05
Risperidone	2.59	0.97	–1.62[d]	0.06
Quetiapine	2.84	1.09	–1.39	0.11
Haloperidol	3.18	1.00	–1.04	0.11
Positive symptoms				
Olanzapine	2.05	1.06	–1.74[d]	0.05
Risperidone	2.15	1.05	–1.64[d]	0.06
Quetiapine	2.31	1.33	–1.44	0.12
Haloperidol	2.70	1.17	–1.16	0.11
Negative symptoms				
Olanzapine	2.36	1.09	–1.58[b,d]	0.05
Risperidone	2.56	1.05	–1.38[d]	0.06
Quetiapine	2.70	1.20	–1.25	0.12
Haloperidol	3.03	1.14	–0.88	0.11
Depressive symptoms				
Olanzapine	2.01	1.04	–1.38[b,d]	0.05
Risperidone	2.14	1.07	–1.21[d]	0.06
Quetiapine	2.37	1.04	–1.06	0.12
Haloperidol	2.52	1.26	–0.73	0.11
Cognitive symptoms				
Olanzapine	2.26	1.08	–1.34[b,d]	0.05
Risperidone	2.44	1.04	–1.17[d]	0.06
Quetiapine	2.52	1.21	–1.05	0.12
Haloperidol	2.99	1.22	–0.64	0.11

[a]The Clinical Global Impression–Schizophrenia scale is scored from 1 (normal) to 7 (severely ill). p Values and least squares mean values were obtained from analysis of variance models with adjustments for baseline covariates, including the baseline value of the symptom domain being analyzed.
[b]$p \leq .001$ vs. risperidone.
[c]$p \leq .001$ vs. quetiapine.
[d]$p \leq .001$ vs. haloperidol.
Abbreviation: SEM = standard error of the mean.

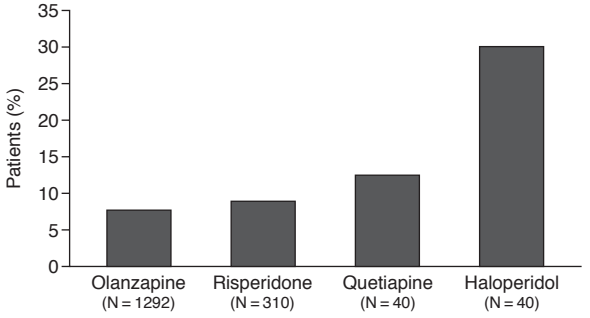
treatment period was highest in the olanzapine group (64.9%, 1350/2080) followed by the risperidone (58.4%, 354/606), quetiapine (46.3%, 38/82), and haloperidol (38.2%, 42/110) treatment groups. The odds of being minimally symptomatic were significantly higher for the olanzapine group compared to patients in each of the other treatment groups: risperidone (OR = 1.39, 95% CI = 1.14 to 1.68; $p \leq .001$), quetiapine (OR = 2.27, 95% CI = 1.43 to 3.59; $p \leq .001$), and haloperidol (OR = 3.26, 95% CI = 2.16 to 4.91; $p \leq .001$). The risperidone group also had significantly higher odds of being minimally symptomatic compared to the haloperidol group (OR = 2.35, 95% CI = 1.52 to 3.62; $p \leq .001$).

There was a general improvement in the clinical status of the cohorts during the 12-month treatment period, as shown by the reduction in symptom scores relative to baseline (Table 3). Olanzapine-treated patients showed a significantly greater improvement in overall symptoms compared to patients in the other 3 treatment groups ($p \leq .001$). The olanzapine group also showed significantly greater improvements in negative, depressive, and cognitive symptoms compared to the risperidone and haloperidol treatment groups ($p \leq .001$). Risperidone-treated patients had a significantly greater improvement in overall symptoms and in all symptom domains compared to haloperidol-treated patients ($p \leq .001$).

Relapse

The risk of relapse between 3 and 12 months was lower with atypical antipsychotic treatment compared to haloperidol treatment, with statistically significant differences evident for olanzapine and risperidone (Figure 2). Based on the subset of patients who had an initial response to antipsychotic monotherapy treatment, the proportion of patients who subsequently relapsed between 3 and 12 months was lowest in the olanzapine group (7.7%) followed by the risperidone group (9.0%) and was the highest in the haloperidol group (30.0%). This difference represents a greater than 6-fold decrease in the odds of relapse when patients were treated with olanzapine compared to haloperidol ($p \leq .001$). The risperidone-treated patients were also significantly less likely to relapse compared to patients in the haloperidol group (OR = 0.16, 95% CI = 0.07 to 0.37; $p \leq .001$). Quetiapine had lower odds of relapse compared to haloperidol (OR = 0.27, 95% CI = 0.08 to 0.90; $p = .03$); however, the difference did not reach the a priori level of significance. The pattern between treatments for the proportion of patients who re-

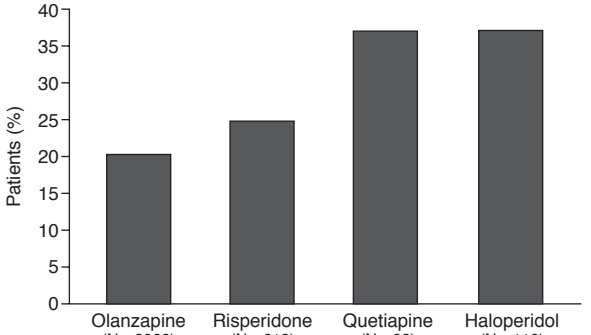
Figure 2. Proportion of Patients Treated With Olanzapine, Risperidone, Quetiapine, or Haloperidol Who Relapsed Between 3 and 12 Months After an Initial Response[a]



	Olanzapine (N = 1292)	Risperidone (N = 310)	Quetiapine (N = 40)	Haloperidol (N = 40)
Patients (%)	7.7	9.0	12.5	30.0
Odds ratio	1[b]	1.07[b]	1.76	6.57
95% CI	NA	0.68 to 1.68	0.66 to 4.74	3.10 to 13.93

[a]Odds ratios are compared to olanzapine, from logistic regression models adjusted for baseline values.
[b]$p \leq .001$ vs. haloperidol.
Abbreviations: CI = confidence interval, NA = not applicable.

Figure 3. Proportion of Patients in the Olanzapine, Risperidone, Quetiapine, and Haloperidol Groups Who Worsened During the 12-Month Treatment Period[a]



	Olanzapine (N = 2066)	Risperidone (N = 612)	Quetiapine (N = 92)	Haloperidol (N = 116)
Patients (%)	20.2	24.8	37.0	37.1
Odds ratio	1[b,c]	1.29	2.28	2.37
95% CI	NA	1.04 to 1.59	1.47 to 3.54	1.60 to 3.52

[a]Odds ratios are compared to olanzapine, from logistic regression models adjusted for baseline values.
[b]$p \leq .001$ vs. quetiapine.
[c]$p \leq .001$ vs. haloperidol.
Abbreviations: CI = confidence interval, NA = not applicable.

lapsed at the 12-month visit was generally consistent with observations made between 3 and 12 months (Table 2 and Figure 2). However, only patients treated with olanzapine had significantly lower odds of experiencing relapse at 12 months compared to haloperidol ($p \leq .001$).

The risk of worsening was significantly lower with olanzapine treatment compared to treatment with quetiapine or haloperidol. The proportion of patients whose symptoms had worsened during the 12-month treatment period was lowest in olanzapine-treated patients (20.2%) and highest in quetiapine- (37.0%) and haloperidol-treated (37.1%) patients (Figure 3). Patients in the quetiapine and haloperidol treatment groups had approximately double the odds of clinically worsening during 12 months relative to the olanzapine group ($p \leq .001$).

As a complement to these measures of treatment effectiveness, hospitalization rate during the 12-month observation period was assessed for all patients with available data. Olanzapine-treated patients had the lowest proportion of inpatient admissions (8.6%, 171/1995) during this period, followed by patients treated with risperidone (10.2%, 58/570), quetiapine (16.1%, 14/87), and haloperidol (24.6%, 28/114). When results were adjusted for baseline covariates (including number of inpatient admissions in the 6 months prior to study enrollment), the odds of admission to an inpatient facility were significantly greater ($p \leq .001$) for patients treated with haloperidol when compared to patients treated with olanzapine or risperidone.

Treatment Compliance

During the 12-month treatment period, patient perception of treatment compliance differed significantly between the groups. Compliance was significantly higher in the olanzapine (85.4%, 1637/1916) and risperidone (81.4%, 445/547) groups compared to the haloperidol (59.5%, 72/121) group ($p \leq .001$; OR comparison). Patient perception of compliance to quetiapine treatment was lower (72.6%, 61/84) than that observed for the other atypical antipsychotics, but the difference did not reach the a priori level of significance (OR comparison).

Substance and Alcohol Abuse/Dependence

On average, less than 1% of patients enrolled in this study reported substance abuse or dependence at baseline (olanzapine = 1.4%, 38/2638; risperidone = 1.3%, 11/860; quetiapine = 0.7%, 1/142; haloperidol = 0.5%, 1/187). However, incidence of substance abuse increased for all treatment groups over the 12-month treatment period. The proportion of patients who reported substance abuse during this time was significantly lower ($p \leq .001$; OR comparison) among patients receiving olanzapine (4.7%, 94/2012) or risperidone (4.6%, 26/565) compared to those receiving haloperidol (11.8%, 13/110). The proportion of patients reporting substance abuse in the quetiapine group (11.5%, 10/87) was comparable to that in the haloperidol group, but differences between quetiapine and the other atypical antipsychotics did not reach statistical significance. The proportion of patients reporting alcohol abuse was 14.4% in the haloperidol group (16/111), 9.5% in the quetiapine group (8/84), 6.7% in the risperidone group (38/565), and 5.5% in the olanzapine group (111/2014). Overall, there was no statistically significant difference in the level of alcohol abuse between the treatment groups.

Table 4. Presence of Adverse Events Associated With Antipsychotics at 12 Months and After Baseline up to 12 Months

Adverse Event	Present at 12 Months N/Total N	%	Present During 12 months N/Total N	%	OR[a] (95% CI) of Adverse Event During 12 Months
Extrapyramidal symptoms					
Olanzapine	106/1980	5.4	361/2061	17.5	1[b,c] (NA)
Risperidone	126/554	22.7	304/646	47.1	4.87[c] (3.95 to 6.00)
Quetiapine	5/80	6.3	13/86	15.1	0.86[b,c] (0.46 to 1.62)
Haloperidol	52/104	50.0	118/153	77.1	23.71 (15.55 to 36.15)
Tardive dyskinesia					
Olanzapine	29/1978	1.5	101/2010	5.0	1[b,c] (NA)
Risperidone	27/554	4.9	66/577	11.4	3.04[c] (2.00 to 4.63)
Quetiapine	4/81	4.9	6/82	7.3	1.45 (0.48 to 4.34)
Haloperidol	10/104	9.6	22/112	19.6	10.50 (5.61 to 19.67)
Loss of libido					
Olanzapine	474/1882	25.2	977/2104	46.4	1[b,c] (NA)
Risperidone	198/528	37.5	396/660	60.0	2.05 (1.67 to 2.52)
Quetiapine	24/79	30.4	53/97	54.6	1.16[c] (0.72 to 1.85)
Haloperidol	52/103	50.5	92/135	68.1	3.25 (2.14 to 4.92)
Impotence/sexual dysfunction					
Olanzapine	280/1657	16.9	575/1795	32.0	1[b,c] (NA)
Risperidone	113/448	25.2	249/541	46.0	2.17 (1.72 to 2.73)
Quetiapine	14/67	20.9	34/79	43.0	1.26 (0.74 to 2.14)
Haloperidol	28/85	32.9	56/107	52.3	3.04 (1.94 to 4.74)
Amenorrhea/menstrual disturbances[d]					
Olanzapine	107/753	14.2	240/814	29.5	1[b,c] (NA)
Risperidone	51/218	23.4	109/259	42.1	2.26 (1.63 to 3.15)
Quetiapine	3/40	7.5	9/43	20.9	0.46[b,c] (0.20 to 1.05)
Haloperidol	11/38	28.9	28/52	53.8	4.06 (2.20 to 7.51)

[a]ORs are for comparisons with olanzapine. p Values were obtained from logistic regression models adjusted for baseline values, including the baseline status of the variable being analyzed.
[b]$p \leq .001$ vs. risperidone.
[c]$p \leq .001$ vs. haloperidol.
[d]Female patients aged ≤ 55 years only.
Abbreviations: CI = confidence interval, NA = not applicable, OR = odds ratio.

Tolerability

During the 12-month treatment period, significant differences were evident between the treatment groups in terms of tolerability. The odds of experiencing extrapyramidal symptoms, tardive dyskinesia, or an adverse event related to sexual functioning were significantly lower in the olanzapine group compared to the risperidone and haloperidol groups ($p \leq .001$) (Table 4).

Patients in the quetiapine group had lower odds of experiencing extrapyramidal symptoms and menstrual disturbances compared to both the risperidone and haloperidol treatment groups ($p \leq .001$). Quetiapine-treated patients also had lower odds of suffering from a loss of libido compared to haloperidol-treated patients ($p \leq .001$). Analyses on potential differences between treatments for the incidences of galactorrhea and gynecomastia were not conducted due to small sample sizes and low frequencies of these events.

The increase in weight from baseline to 12 months differed between treatment groups (olanzapine: least squares mean = 3.4 kg, 95% CI = 2.9 to 4.0 kg; risperidone: least squares mean = 2.2 kg, 95% CI = 1.5 to 3.0 kg; quetiapine: least squares mean = 1.9 kg, 95% CI = 0.5 to 3.3 kg; haloperidol: least squares mean = 2.2 kg, 95% CI = 0.9 to 3.4 kg), with significantly greater increase in weight for olanzapine compared with risperidone ($p < .001$) and nonsignificantly greater increase for olanzapine compared with quetiapine ($p = .024$) and haloperidol ($p = .032$). The proportion of patients who gained more than 7% of their baseline body weight by the 12-month visit was 39% (760/1963) for olanzapine-treated patients, 28% (153/549) for risperidone-treated patients, 25% (20/80) for quetiapine-treated patients, and 26% (27/105) for haloperidol-treated patients. Patients treated with risperidone had significantly lower odds of gaining more than 7% of their baseline body weight compared to patients treated with olanzapine (OR = 0.60, 95% CI = 0.48 to 0.74; $p \leq .001$). Similar results were found when olanzapine was compared with quetiapine (OR = 0.55, 95% CI = 0.32 to 0.94; $p = .030$) and haloperidol (OR = 0.51, 95% CI = 0.32 to 0.81; $p = .004$).

DISCUSSION

Relapse prevention is critically important in the long-term management of schizophrenia. Our study has shown that patients treated with atypical antipsychotics, particularly olanzapine and risperidone, are less likely to experi-

ence a relapse of symptoms when compared with patients treated with haloperidol. In this study, olanzapine and risperidone treatment were associated with a greater than 6-fold reduction in the odds of relapse compared to haloperidol treatment. The results of this large, observational study support findings from randomized clinical trials, which have shown that the efficacy of atypical antipsychotics is equal or superior to that of typical antipsychotics.[11,12,18–20]

To the best of our knowledge, this is the first comprehensive global study to directly compare rates of relapse in patients treated with atypical antipsychotics. During a 12-month treatment period, relapse rates differed between olanzapine, quetiapine, and risperidone, but the differences were not statistically significant. Relapse rates for olanzapine and risperidone were generally comparable and lower than the relapse rate associated with quetiapine treatment. Whether these initial differences are maintained or increased during the 3-year study period will be of considerable clinical interest, given the impact of relapse on patients' quality of life and health care costs.[18,21] Relating the comparative relapse rates for atypical antipsychotics in our study to the published literature is difficult given the noted absence of other direct comparator studies between atypical antipsychotics for relapse[11,22] and the different definitions of relapse used in other studies.[11,21] However, based on recently published relapse rates in studies comparing atypicals with typicals or placebo, our relapse rates are within the range of or close to those reported for olanzapine (4%–22%),[11] risperidone (6%–25%),[11] and haloperidol (19%–40%).[11,12,18]

Although the relative effects of atypical antipsychotics on relapse are clinically important, the success of maintenance therapy for schizophrenia is also influenced by other outcomes related to efficacy and tolerability.[21] In terms of efficacy and tolerability outcomes, significant differences were evident between the new antipsychotic treatments. Olanzapine treatment was associated with significantly better outcomes than both risperidone and quetiapine for a number of symptom endpoints (e.g., response at 12 months, overall symptoms, minimally symptomatic status). The results of this study also indicate that when compared to patients who received haloperidol, patients treated with olanzapine or risperidone experienced lower odds of inpatient admission during the 12-month observation period.

This study has also shown that olanzapine treatment resulted in significantly lower odds of experiencing extrapyramidal symptoms, tardive dyskinesia, and adverse events related to sexual functioning when compared with risperidone. In our study, treatment with quetiapine resulted in a lower risk for extrapyramidal symptoms and menstrual disturbances when compared to treatment with risperidone. The tolerability differences that we observed confirm the results of previous long-term, prospective, comparative studies, which have shown lower incidences of extrapyramidal symptoms[23,24] and tardive dyskinesia[24] with olanzapine compared to risperidone. When compared to risperidone, a lower frequency of tardive dyskinesia was observed with olanzapine based on Abnormal Involuntary Movement Scale score, but was not detected in the frequency of spontaneously reported tardive dyskinesia adverse events.[24] In terms of weight gain, we have shown that the atypical antipsychotics differed from each other and that olanzapine-treated patients gained more weight than patients treated with risperidone. Change in weight with atypical and typical antipsychotic treatments and the influence of baseline body mass index on weight change are important, topical issues and will be the focus of a separate report.

The differences that we observed between treatment groups in relapse rates are consistent with the previously reported advantage of atypical antipsychotics over conventional typical antipsychotics.[18,20] In our study, treatment with olanzapine and risperidone was associated with significantly greater improvements in all measures of clinical status when compared to treatment with haloperidol. In addition, more patients achieved or maintained minimally symptomatic status when treated with olanzapine or risperidone compared to haloperidol. Although not a statistically significant difference, the relapse rate was numerically lower for patients treated with olanzapine when compared to patients treated with risperidone. However, a recent meta-analysis of data from 3 double-blind studies indicated that relapse rates may differ between atypical antipsychotics, with olanzapine-treated patients significantly less likely to relapse than patients treated with risperidone, quetiapine, or ziprasidone.[25]

The better performance observed in patients treated with olanzapine or risperidone compared to haloperidol may also be partially due to improved compliance. Patients in the olanzapine and risperidone groups were significantly more compliant with their treatment regimen than patients in the haloperidol group. Treatment adherence can be affected by the tolerability to the medication,[10,26] which in turn can be affected by the dose. The doses used in our study were comparable to those reported previously in studies with olanzapine, risperidone, quetiapine, or haloperidol.[12,18,23,27] Geddes and colleagues[28] have argued that haloperidol may be at a disadvantage relative to the atypicals when the haloperidol dose exceeds 12 mg/day. The mean dose of haloperidol used in this study was only slightly below this threshold (11.8 ± 8.8 mg/day) and may be at least partially responsible for the advantage demonstrated by atypicals in terms of tolerability or adherence.[28]

Substance and alcohol abuse are key predictors of schizophrenic relapse.[21,29] In our study, a significantly higher proportion of patients in the haloperidol group were substance abusers compared to patients in the olan-

zapine group. However, we do not feel that this is likely to fully account for the higher relapse rate among haloperidol-treated patients. In contrast to studies in Westernized countries, where approximately half of patients with schizophrenia are reported to be substance abusers,[30] the actual proportion of patients who were substance abusers in our study was relatively low (5%–12%). Differences between treatments are therefore unlikely to be explained by a relatively small subset of patients who were substance abusers. The lower rates of substance abuse in our study concur with the lower prevalence of substance abuse reported in developing countries compared to developed countries.[31] Our study was not confounded by including a higher proportion of males, a factor associated with a higher rate of substance abuse.[21]

In terms of the study design, IC-SOHO has both strengths and limitations. IC-SOHO incorporated a pragmatic design to closely reflect the real-life clinical situation. Numerous researchers have emphasized the need for clinical practice studies that compare the clinical effectiveness of atypical antipsychotics.[11,12,22,23,27] Our clinical practice study involved a heterogeneous population of patients, including those with substance or alcohol abuse. Furthermore, psychiatrists were able to choose the most appropriate treatment and optimize the dose. Importantly, the study was prospective in design, included a large sample size with broad geographic coverage, and is of long-term duration. Some of the limitations of this study, as previously discussed,[14] are intrinsically associated with observational studies. The potential for bias due to lack of blinding and randomization was reduced in this study by adjusting comparisons using baseline covariates that were recognized to have clinical significance. However, we acknowledge that these baseline corrections may not fully address the potential biases due to the design of this study. We also recognize that the sample selected for the current analyses could be criticized in terms of selection bias. However, we believe that selecting patients on the basis of their compliance to a specific treatment was a reasonable and clinically meaningful way to attribute outcomes to a specific treatment. Notably, the relative order of effect between treatments for response and relapse rates (most to least favorable: olanzapine, risperidone, quetiapine, haloperidol) was generally consistent with that observed when we repeated the analyses using data from all patients who were prescribed monotherapy at baseline (data not reported in this article).

Other limitations related to the IC-SOHO study include the relatively low dose and small sample size for the quetiapine treatment group. The dosage of quetiapine used in IC-SOHO was in accordance with the prescribing information available at the time of the study. Importantly, the dose of quetiapine was also able to be adjusted at the discretion of the treating psychiatrist. Studies with quetiapine, subsequent to those on which the prescribing information was based, now indicate that doses of at least 600 mg/day may be required to achieve optimal efficacy.[32–34] In terms of applying the results from IC-SOHO to other populations, caution should be exercised. Even though IC-SOHO is being conducted in many centers around the world, our results may not be directly applicable to other patient groups (e.g., patients on combination treatments, inpatients). Differences in psychosocial factors and practice patterns between developing and developed countries could also limit the ability to generalize our findings.[21]

In conclusion, this study has shown that 12 months of treatment with atypical antipsychotics, particularly olanzapine and risperidone, is more effective in preventing relapse than haloperidol. Although the differences between the atypical antipsychotics in preventing relapse during the initial 12 months of treatment were relatively moderate, significant differences were apparent between the atypical antipsychotics in other measures of clinical effectiveness and tolerability. The pragmatic design and naturalistic setting of this large, intercontinental study reinforce the clinical relevance of these results.

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

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