A Practical Clinical Trial Comparing Haloperidol, Risperidone, and Olanzapine for the Acute Treatment of First-Episode Nonaffective Psychosis

Benedicto Crespo-Facorro, M.D., Ph.D.; Rocío Pérez-Iglesias, M.D., Ph.D.; MariLuz Ramirez-Bonilla, M.D.; Obdulia Martínez-García, B.S.N.; Javier LLorca, M.D., Ph.D.; and José Luis Vázquez-Barquero, M.D., Ph.D.

Objective: Randomized controlled drug trials have demonstrated that antipsychotic medication is effective to rapidly improve psychotic symptomatology in first-episode psychosis. However, these results may not be generalizable to routine clinical practice. We evaluated the effectiveness, tolerability, and safety of olanzapine, risperidone, and haloperidol in individuals with first-episode nonaffective psychosis who are representative of clinical practice and who are treated in routine clinical settings.

Method: 172 patients participated in a practical clinical trial and were randomly assigned to haloperidol (N = 56), risperidone (N = 61), and olanzapine (N = 55). The mean modal daily doses were 5.4 mg/day for haloperidol, 4 mg/day for risperidone, and 15.3 mg/day for olanzapine; 98.3% of subjects were drug naive at baseline. Data from clinical measures of treatment response and tolerability and safety data from the 6-week acute phase of a large epidemiologic and longitudinal (February 2001 to February 2005) intervention program of first-episode psychosis (schizophrenia spectrum disorders, DSM-IV criteria) are reported.

Results: All 3 treatments showed similar effectiveness in reducing the severity of general, negative, and positive symptomatology after 6 weeks of treatment, as reported by mean change in total Clinical Global Impressions-Severity of Illness scale, Brief Psychiatric Rating Scale (BPRS), Scale for the Assessment of Positive Symptoms, and Scale for the Assessment of Negative Symptoms scores between baseline and 6 weeks. The proportion of study subjects responding, defined as 40% or greater BPRS total score improvement from baseline, was 57.1% (N = 32 of 56) haloperidol, 52.5% (N = 32 of 61) risperidone, and 63.6% (N = 35 of 55) olanzapine, with no statistical differences among groups. The frequency of extrapyramidal symptoms ($\chi^2 = 24.519$; $p < .001$) and concomitant anticholinergic medication use ($\chi^2 = 57.842$; $p < .0001$) was greater with haloperidol than olanzapine or risperidone. Olanzapine-treated patients had significantly more weight gain compared with the haloperidol and risperidone groups ($p < .001$).

Conclusion: Relatively low doses of haloperidol, risperidone, and olanzapine are equally effective for the acute treatment of first-episode nonaffective psychosis under usual conditions of real clinical practice.

(J Clin Psychiatry 2006;67:1511–1521)

Received Jan. 8, 2006; accepted March 13, 2006. *From the University Hospital Marqués de Valdecilla, Department of Psychiatry (Drs. Crespo-Facorro, Pérez-Iglesias, Ramirez-Bonilla, and Vázquez-Barquero and Ms. Martínez-García) and Department of Preventive Medicine and Public Health (Dr. LLorca), School of Medicine, University of Cantabria, Santander, Spain.*

The present study was performed at the Hospital Marqués de Valdecilla, University of Cantabria, Santander, Spain, under the following grant support: Instituto de Salud Carlos III, FIS 00/3095 and SENY Fundatió Research Grant CI 2005-0308007, Fundación Marqués de Valdecilla A/02/07. The Mental Health Services of Cantabria provided funding for implementing the program.

Presented in part at the International Congress on Schizophrenia Research, March 29–April 2, 2003, Colorado Springs, Col., and April 2–6, 2005, Savannah, Ga.

The authors report no other financial affiliations relevant to the subject of this article.

Corresponding author and reprints: Benedicto Crespo-Facorro, M.D., Ph.D., Hospital Universitario Marqués de Valdecilla, Department of Psychiatry, Planta 2ª, Edificio 2 de Noviembre. Avda. Valdecilla s/n, 39008, Santander, Spain (e-mail: bcfacorro@humv.es).

The first treatment intervention in drug-naive patients with a first episode of schizophrenia is critical to provide an optimal prognosis of the illness.[1] The rapidity and maintenance of treatment response as well as good tolerability and so a better adherence are crucial factors for ensuring successful care.[2,3]

Randomized controlled drug trials have shown that adequate treatment with antipsychotic medication is associated with a rapid improvement of active psychotic symptomatology in individuals with a first episode of psychosis.[4–8] Young patients suffering from a first break of psychoses seem to be highly responsive to low doses of antipsychotics[9] and more sensitive to extrapyramidal side effects[10] and to acute weight gain.[11] Both second-generation antipsychotics (SGAs) and low doses of first-generation antipsychotics (FGAs) have been demonstrated, in randomized, double-blind, controlled trials, to be similarly efficacious in safely ameliorating active psychotic symptomatology in the early stages of the illness.[12,13] The SGAs, based on their real advantage regarding the low rate of emergent extrapyramidal side effects, have become the most commonly used class of antipsychotics in clinical practice in the treatment of first episodes.[14–16] However, the SGAs do cause a host of meta-

bolic consequences, which have the potential to surpass the negative impact of motor adverse effects.[12,17] Thus, the selection of antipsychotic is mostly determined by the profile of side effects of the medications, and the differences among antipsychotics in terms of effectiveness, safety, and tolerability have expectedly turned out to be a topic of increasing research interest.

The results yielded from randomized controlled trials may not be generalizable to routine clinical practice.[18] Those individuals who agree to participate in trials may not be representative of the patients treated in routine clinical practice or of the general population of individuals suffering from schizophrenia.[19] The priority in psychiatry of conducting non–industry-funded clinical trials to enhance the generalizability of the findings from clinical research has been recently emphasized by a range of stakeholders. Such trials are necessary to accurately evaluate clinically relevant interventions in typically heterogeneous and representative samples of community patients and so to aid decision makers who are faced with clinical choices in routine clinical practice.[20]

Practical clinical trials addressing the issue of the effectiveness and safety of low doses of FGAs and SGAs during the early phases of the illness may aid practicing clinicians to select the appropriate initial antipsychotic treatment in patients with a first-episode nonaffective psychosis. The purpose of the present study was to evaluate the effectiveness, tolerability, and safety of SGAs (olanzapine and risperidone) and FGAs (haloperidol) in the acute treatment of individuals with first-episode nonaffective psychosis who are representative of clinical practice in an epidemiologic catchment area and who are treated in routine clinical community settings.

METHOD

Study Setting and Financial Support

The data for these analyses were taken from the 6-week acute phase of a large epidemiologic and longitudinal (3 years) intervention program of first-episode psychosis (Clinical Program of First Episode Psychosis; PAFIP) carried out in the region of Cantabria, Spain. The study was conducted at the outpatient clinic and the inpatient unit at the University Hospital Marqués de Valdecilla, which is located in Santander (Cantabria) and serves an epidemiologic catchment area population of 555,000 people.

A divulgation process within all mental health outpatient units in Cantabria (5 outpatient clinics) and family physicians' practices was thoroughly carried out during 3 months prior to starting the program to enhance referrals. Referrals to the PAFIP come from the inpatient unit and emergency room at the University Hospital Marqués de Valdecilla, community mental health services, and other community health care workers in the entire region of Cantabria. Thus, we do not think there were biases in the way patients were referred. The age-corrected (15–50 years) incidence rate for schizophrenia spectrum disorder was 1.52 per 10,000 inhabitants. After the initial contact by a qualified psychiatric nurse with the source of referral, an experienced psychiatrist carried out a formal interview for a full assessment of the patient and to confirm the presence of a nonaffective psychotic disorder (DSM-IV criteria).

The Mental Health Services of Cantabria provided funding for implementing the program. No pharmaceutical company supplied any financial support to the study. The study was designed and directed by B.C.-F. and J.L.V.-B. The study conformed to international standards for research ethics and was approved by the local institutional review board.

Subjects

From February 2001 to February 2005, all referrals to PAFIP were screened for the following criteria: (1) age 15 to 60 years; (2) DSM-IV criteria for a principal diagnosis of schizophreniform disorder, schizophrenia, schizoaffective disorder, brief reactive psychosis, schizotypal personality disorder, or psychosis not otherwise specified; (3) habitually living in the catchment area; (4) no prior treatment with antipsychotic medication or, if previously treated, a total lifetime of adequate antipsychotic treatment of less than 6 weeks; and (5) current psychotic symptoms of moderate severity or greater assessed by 1 of the 5 items of the Scale for the Assessment of Positive Symptoms (SAPS).[21] Patients meeting these criteria and their families provided written informed consent to be included in the PAFIP. The diagnoses were confirmed according to the DSM-IV criteria using the Structured Clinical Interview for DSM-IV (SCID-I)[22] by an expert psychiatrist (M.R.-B.) 6 months after the initial contact. Only those patients with diagnoses of mental retardation (DSM-IV criteria) or drug dependence (DSM-IV criteria) were not included and, although they were initially treated to control the acute phase of the psychosis, they were eventually remitted to specific psychiatric settings.

Study Design and Procedures

The medication protocol was explained to the patient and family by the psychiatrist. At baseline, 98.3% of subjects (N = 169) had not previously received antipsychotic treatment. The patients (N = 3) who were receiving antipsychotics at the first contact underwent a washout period of 3 to 5 days after which they were randomly assigned to treatment with risperidone, olanzapine, or haloperidol. For the acute treatment of the illness (6 weeks), patients went through a pharmacologic protocol with no added psychotherapeutic interventions. Dose ranges were 5 to 20 mg/day for olanzapine, 3 to 6 mg/day for risperidone,

and 3 to 9 mg/day for haloperidol. The initial doses were progressively augmented until therapeutic effects were obtained. The medication doses could be adjusted as clinically indicated within the prescribed range, with the aim of targeting the lowest effective dose while still enabling patients to receive active treatment. Patients were assessed for clinical improvement and the occurrence of side effects at baseline and at 1, 2, 3, 4, and 6 weeks. Certain concomitant medications (i.e., lormetazepam and clonazepam) were permitted for the management of agitation, general behavior disturbances, and/or insomnia. If clinically significant extrapyramidal signs occurred, anticholinergic medication (biperiden at a dose of up to 8 mg/day) was allowed. We did not prophylactically administer antiparkinsonian medications. Antidepressants (sertraline) and mood stabilizers (lithium) were permitted in the acute treatment phase if clinically needed.

The patients were defined as nonresponders to the optimum dose of antipsychotic during 6 weeks if they had a less than 40% reduction of the Brief Psychiatric Rating Scale[23] (BPRS) score at intake and had a Clinical Global Impressions-Severity of Illness[24] scale (CGI-S) score of less than or equal to 4 (moderately ill). Those patients who did not respond at 6 weeks or did not tolerate the initial antipsychotic were changed to a different antipsychotic (atypical or conventional) on the basis of clinical criteria.

Duration of untreated illness (DUI) was defined as the time from the first unspecific symptoms related to psychosis (for such a symptom to be considered, there should be no return to previous stable level of functioning) to initiation of adequate antipsychotic drug treatment. *Duration of untreated psychosis* (DUP) was defined as the time from the first continuous (present most of the time) psychotic symptom to initiation of adequate antipsychotic drug treatment. Age at onset of psychosis was defined as the age at which the first continuous (present most of the time) psychotic symptom emerged.

Assessments

The same clinically experienced and trained rater (B.C.-F.) provided all ratings in all patients to guarantee a high reliability among measurements. To assess the clinical response to treatment with haloperidol, risperidone, and olanzapine, the following scales were utilized:

1. The BPRS[23] assessed the severity of general psychiatric symptomatology.
2. The Scale for the Assessment of Negative Symptoms[25] (SANS) and the SAPS[21] assessed the presence of psychotic, positive, and negative symptoms.
3. The CGI-S[24] measured the overall severity of illness.
4. The Hamilton Rating Scale for Depression[26] (24-item HAM-D), the Calgary Depression Scale[27] (CDS), and the Young Mania Rating Scale[28] (YMRS) evaluated affective symptoms.

To assess general adverse event experiences, the Scale of the Udvalg for Kliniske Undersogelser[29] (UKU) was used. Extrapyramidal signs and abnormal involuntary movements were assessed by examinations of patients and scored on the Simpson-Angus Scale[30] (Simpson-Angus; including an additional dystonia item), the Abnormal Involuntary Movement Scale[31] (AIMS), and the Barnes Akathisia Scale[32] (BAS).

Assessments with the BPRS, SAPS, SANS, and CGI-S and measurements of side effects were completed at baseline, weekly during the first 4 weeks, and at the 6-week study endpoint. Affective symptoms were measured at baseline and at the 6-week study endpoint.

Statistical Methods

All analyses were done on an intent-to-treat basis, meaning that all patients were included in the treatment groups to which they were initially assigned no matter how long they adhered to the protocol. All total scores from rating scales and subscales were derived from the individual scale items. Patients were included in the effectiveness analysis only if they had the baseline measure and at least another measure.

For the analysis of continuous effectiveness and safety data, we used the following 2 approaches: (1) the traditional last-observation-carried-forward analysis-of-variance (ANOVA) model and (2) the analysis of covariance (ANCOVA) with baseline severity as a covariate. Within-group comparisons were also explored by using a t test to analyze baseline-to-endpoint differences. Fisher exact test and χ^2 test were used to evaluate categorical data. All hypotheses were tested by using a 2-sided significance level of .05.

RESULTS

Description of Study Cohort

Of 202 individuals who were referred to PAFIP, 184 met inclusion criteria. Of these, 182 patients gave written consent to study participation and were randomly assigned to treatment. Those patients (N = 18) who did not meet the inclusion criteria but had other diagnoses were referred to their outpatient psychiatric clinics for further evaluation and treatment. Ten of the initial 182 individuals were excluded from the final analyses because they did not meet SCID-I criteria for nonaffective psychosis (N = 7) (5 affective psychosis, 1 social phobia, and 1 personality disorder not otherwise specified) at 6-month interview, or because it was confirmed they had previously received antipsychotic treatment for longer than 6 weeks

  © Copyright 2006 Physicians Postgraduate Press, Inc.

Table 1. Demographic and Clinical Characteristics of 172 Drug-Naive Patients With a First Episode of Psychosis Randomly Assigned to Treatment With Risperidone, Olanzapine, or Haloperidol

	Haloperidol (N = 56)		Olanzapine (N = 55)		Risperidone (N = 61)			
Characteristic	Mean	SD	Mean	SD	Mean	SD	F (df = 2,169)	p
Age at admission, y	28.3	8.7	27.5	6.9	26.1	7.6	1.19	.307
Age at psychosis onset, y	26.8	7.5	26.5	6.8	25.0	7.0	1.06	.348
Duration of illness, mo	32.3	39.7	21.2	33.2	29.9	36.0	1.42	.244
Duration of psychosis, mo	17.8	37.2	12.1	29.1	13.2	21.9	0.59[a]	.558
	N	%	N	%	N	%	χ^2 (df = 2)	p
Diagnosis								
Schizophrenia	41	74.5	29	53.7	33	57.9	5.662	.059
Other schizophrenia spectrum diagnoses	14	25.4	26	46.2	24	42.1		
Sex (male)	36	64.3	33	60.0	38	62.3	0.217	.897
Education level (elementary)	28	50.0	27	49.1	33	54.1	0.335	.846
Socioeconomic status of parents (Not/low qualified worker)[b]	36	64.3	32	58.2	34	58.6	0.543	.762
Urban area (yes)	26	46.4	31	56.4	39	63.9	3.368	.162
Living with parents (yes)	34	60.7	31	56.4	44	72.1	3.350	.187
Unmarried (yes)	47	83.9	43	78.2	55	90.2	3.147	.207
Student (yes)	14	25.0	10	18.2	10	16.4	1.492	.474
Unemployed (yes)	24	42.9	23	41.8	31	50.8	1.154	.562
Family psychiatric history (yes)	13	23.2	15	27.3	6	9.8	6.166	.046
Hospital status inpatient (yes)	41	73.2	35	63.6	33	54.1	4.599	.100

[a]df = 2,166.
[b]Hollingshead-Redlich scale.

(N = 1), or because they only had data from the baseline interview (N = 2). Therefore, the present study is based on data from 172 patients with a first episode of nonaffective psychosis randomly assigned to treatment with haloperidol (N = 56), risperidone (N = 61), and olanzapine (N = 55). This sample size results in sufficient power (80%) to detect statistical significance in change of at least 30% in total change scores of the BPRS between baseline and endpoint assessments, considering an alpha level of 0.05 and standard deviation of 12.

The mean initial doses were 4.1 mg/day for haloperidol, 2.6 mg/day for risperidone, and 9.7 mg/day for olanzapine, and the acute-phase mean modal daily doses were 5.4 mg/day for haloperidol, 4 mg/day for risperidone, and 15.3 mg/day for olanzapine. At baseline, only 1.7% of patients (N = 3) reported some prior treatment. The mean self-reported duration of prior treatment was 4 weeks (SD = 2; range, 2–6).

The dropout rate at 6 weeks was small (N = 7), and there were no differences among treatment groups (N = 1, 1.8% of the haloperidol-treated group; N = 4, 6.6% of the individuals treated with risperidone; and N = 2, 3.6% of the olanzapine-treated subjects) (χ^2 = 1.742; p = .419). Dropout reasons included the following: 4 individuals (2 risperidone-treated, 1 haloperidol-treated, and 1 olanzapine-treated) decided to withdraw from the study, 2 patients (1 olanzapine-treated and 1 risperidone-treated) did not show up for the 6-week interview, and 1 patient (risperidone-treated) switched medication because there was a severe increase in the psychotic symptomatology. The last observations for these patients were at the fourth week in 6 cases and at the 3-week interview in a single case.

Demographic and clinical characteristics of the total sample are shown in Table 1. The mean age of the sample was 27.3 years (SD = 7.74; range, 15.4–56.9), mean age at onset of psychosis was 26.1 years (SD = 7.1; range, 14.8–53.8), mean length of illness (DUI) was 27.9 months (SD = 36.5; range, 0.3–210; median = 15), and mean length of psychosis (DUP) was 14.3 months (SD = 29.8; range, 0.2–204; median = 4); 62.2% were men and 63.4% required hospitalization. All (N = 171) but 1 patient (who was Hispanic) were white. At 6 months, their diagnoses according to the SCID-I were schizophrenia (N = 105; 61%), schizophreniform disorder (N = 35; 20.3%), schizoaffective disorder (N = 5; 2.9%), psychosis not otherwise specified (N = 13; 7.6%), brief reactive psychosis (N = 7; 4.1%), and schizotypal personality disorder (N = 1; 0.6%). In 6 of the 172 randomized patients, we could not confirm their DSM-IV criteria initial diagnosis (N = 3, schizophrenia; N = 2, schizophreniform disorder; and N = 1, brief reactive psychosis) at 6 months because they dropped out of the study. No statistical differences were found between the 3 treatment groups in any of the background demographic and clinical characteristics (Table 1).

Effectiveness

Endpoint analysis. The analysis of the psychopathology scale scores is described in Table 2 and Figure 1. Baseline scores and mean change from baseline to endpoint on the total BPRS, total SAPS, total SANS, and CGI-S (global impression) scores, along with 95% confidence intervals, are shown in Table 2. There were no statistically significant differences in the severity of symptoms among the 3 treatment groups at baseline.

Table 2. Changes in Psychopathology From Baseline to Endpoint Among 172 Drug-Naive Patients With a First Episode of Psychosis Randomly Assigned to Treatment With Risperidone, Olanzapine, or Haloperidol

	Haloperidol (N = 56)		Olanzapine (N = 55)		Risperidone (N = 61)			
Variable	Mean	SD	Mean	SD	Mean	SD	F (df = 2,169)	p
Clinical Global Impressions-Severity of Illness scale score								
Baseline	6.3	0.7	6.0	0.8	6.1	0.7	1.901	.153
6 weeks	3.8	1.0	3.8	1.1	3.8	1.0	0.121	.886
6-week change from baseline[a]	–2.5[c]	1.0	–2.2[c]	1.1	–2.2[c]	1.0	1.335	.266
6-week change from baseline[b]	–2.4	0.1	–2.3	0.1	–2.2	0.1	0.531	.589
Brief Psychiatric Rating Scale total score								
Baseline	62.4	10.9	59.9	12.1	56.8	10.3	3.820	.024
6 weeks	37.1	13.3	35.4	9.4	35.1	9.2	0.564	.580
6-week change from baseline[a]	–25.3[c]	14.1	–24.5[c]	14.9	21.6[c]	12.0	1.186	.308
6-week change from baseline[b]	–23.1	1.4	–24.2	1.4	–23.9	1.4	0.161	.851
Scale for the Assessment of Negative Symptoms score								
Baseline	6.7	6.0	7.5	6.2	7.4	6.2	0.258	.773
6 weeks	5.6	4.6	4.1	4.7	5.3	5.2	1.476	.198
6-week change from baseline[a]	–1.1	6.5	–3.3[c]	6.0	–2.1[c]	5.3	2.010	.137
6-week change from baseline[b]	–1.4	0.6	–3.2	0.6	–2.0	0.6	2.348	.099
Scale for the Assessment of Positive Symptoms score								
Baseline	13.7	3.7	12.4	4.6	12.0	4.0	1.274	.282
6 weeks	3.9	4.5	3.4	3.2	3.4	3.8	0.371	.691
6-week change from baseline[a]	–9.7[c]	4.9	–9.0[c]	4.8	–9.6[c]	4.3	0.387	.679
6-week change from baseline[b]	–9.3	0.5	–9.4	0.5	–9.6	0.5	0.130	.878
Hamilton Rating Scale for Depression score								
Baseline	12.2	5.8	13.4	6.4	11.8	6.3	1.094*	.337
6 weeks	6.6	6.1	5.1	5.3	5.6	4.9	1.097**	.336
6-week change from baseline[a]	–5.5[c]	8.4	–8.3[c]	6.8	–5.8[c]	7.5	2.048***	.132
6-week change from baseline[b]	–5.6	0.7	–7.3	0.8	–6.6	0.7	1.360***	.260
Calgary Depression Scale score								
Baseline	1.9	2.5	2.2	3.1	1.8	2.5	0.455*	.635
6 weeks	1.8	2.9	1.1	2.4	0.9	2.3	1.605**	.204
6-week change from baseline[a]	–0.1	3.6	–1.2	3.3	–0.7	3.0	1.374***	.256
6-week change from baseline[b]	–0.1	0.3	–0.9	0.3	–0.9	0.3	1.748***	.177
Young Mania Rating Scale score								
Baseline	9.3	4.3	9.2	4.7	8.8	4.8	0.197*	.821
6 weeks	2.8	4.4	2.4	2.5	2.6	3.2	0.160**	.852
6-week change from baseline[a]	–6.4[c]	4.5	–6.6[c]	4.9	–5.9[c]	4.8	0.329***	.720
6-week change from baseline[b]	–6.1	0.5	–6.5	0.5	–6.2	0.4	0.162***	.850

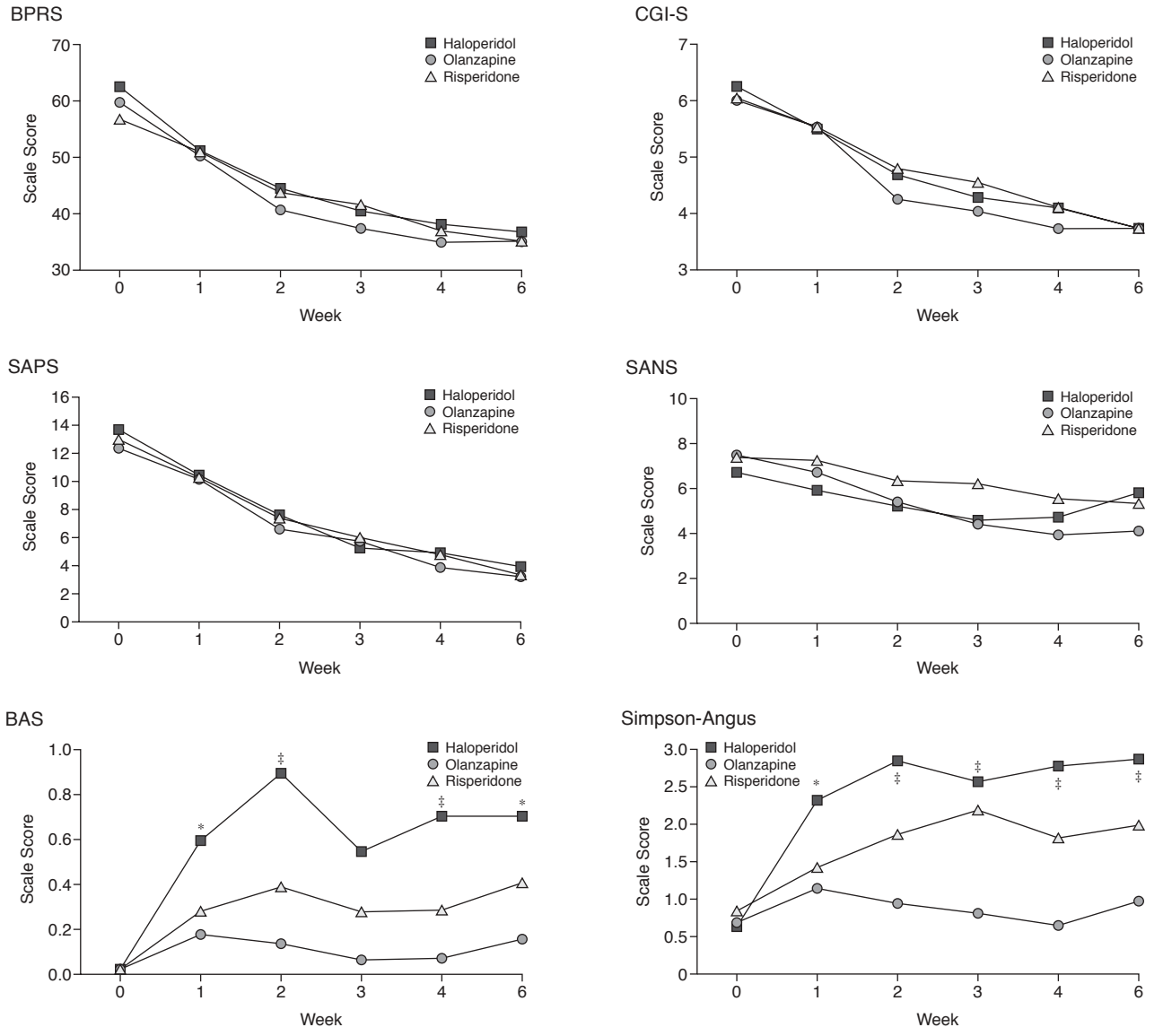
[a]Results of the analysis-of-variance model for determining 6-week change from baseline.
[b]Results of the analysis of covariance with baseline severity as covariate for determining 6-week change from baseline.
[c]Significant within-group improvement from baseline with paired t test ($p < .01$).
*df = 2,165.
**df = 2,161.
***df = 2,158.

The ANOVA did not find advantages of any of the 3 treatments, as reported by mean change between baseline in 6-week total scores of the BPRS ($F = 1.186$; $p = .308$), SAPS ($F = 0.387$; $p = .679$), SANS ($F = 2.01$; $p = .137$), and CGI-S ($F = 1.335$; $p = .266$). All treatments have shown their effectiveness in reducing the severity of symptomatology after 6 weeks of treatment, as reported by within-treatment-group reductions (Table 2). Since the severity of negative symptoms may be in part secondary to extrapyramidal side effects or depressive symptoms, we repeated the ANOVA with severity of extrapyramidal symptoms (total score of Simpson-Angus) and depressive symptoms (total score of CDS) at 6 weeks as covariates. The results of the analyses were not essentially affected by these covariates.

The ANOVA did not show statistically significant differences among groups in the reduction of depressive and manic symptoms, as reported by mean change between baseline in 6-week total scores of the HAM-D ($F = 2.048$; $p = .132$), CDS ($F = 1.374$; $p = .256$), and YMRS ($F = 0.329$; $p = .720$).

Response rate analysis. A more robust measure of treatment effectiveness is the clinical response rate. Thus, in the categorical analysis of response rate that used the definition of response, 40% or greater BPRS total improvement from baseline, the proportion of study subjects responding by the sixth week was 57.1% for those taking haloperidol (N = 32 of 56), 52.5% for those assigned to risperidone (N = 32 of 61), and 63.6% for those receiving olanzapine (N = 35 of 55) ($\chi^2 = 1.485$; $p = .476$). The mean time to response was haloperidol, 4.32 weeks (SD = 0.24); risperidone, 4.85 weeks (SD = 0.21); and olanzapine, 4.36 weeks (SD = 0.23), without differences between groups (log-rank test = 2.09; df = 2; $p = .352$).

Figure 1. Psychopathology Severity and Extrapyramidal Side Effect Changes at Weeks 0 to 6 of Patients With a First Episode of Psychosis Treated With Olanzapine, Haloperidol, or Risperidone



*p < .05 in the analysis of variance.
‡p < .01 in the analysis of variance.
Abbreviations: BAS=Barnes Akathisia Scale, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, SANS = Scale for the Assessment of Negative Symptoms, SAPS = Scale for the Assessment of Positive Symptoms, Simpson-Angus = Simpson-Angus Scale.

Despite the low dropout rate in our study, we also conducted a completers-only analysis of effectiveness measures. The results were essentially the same as the last-observation-carried-forward analysis.

Safety

Extrapyramidal symptoms. Treatment-emergent extrapyramidal signs and symptoms, measured using the Simpson-Angus and the BAS, were assessed by both baseline-to-end changes and newly emergent categorical changes. Analyses of variance showed no significant between-treatment differences in extrapyramidal symptoms at baseline on the Simpson-Angus ($F = 0.313$; $p = .732$) (Table 3). The ANOVA showed that baseline-to-end changes were statistically significant among treatment groups ($F = 10.557$; $p < .0001$) (Table 3). We repeated the ANOVA with severity of negative symptoms (total score of SANS) and depressive symptoms (total

Table 3. Changes From Baseline to Endpoint in Severity of Extrapyramidal Symptoms in 172 Drug-Naive Patients With a First Episode of Psychosis Randomly Assigned to Treatment With Risperidone, Olanzapine, or Haloperidol

	Haloperidol (N = 56)		Olanzapine (N = 55)		Risperidone (N = 61)			
Variable	Mean	SD	Mean	SD	Mean	SD	F (df = 2,169)	p
Barnes Akathisia Scale score								
Baseline	0.02	0.13	0.02	0.14	0.02	0.13	0.003	.997
6 weeks	0.68	1.15	0.15	0.62	0.38	0.90	4.746[a]	.010
6-week change from baseline	0.66	1.16	0.13	0.64	0.36	0.91	4.576	.012
Simpson-Angus Scale score								
Baseline	0.63	1.37	0.67	1.42	0.82	1.40	0.313	.732
6 weeks	2.89	3.10	0.93	2.36	1.95	2.40	7.693[b]	.001
6-week change from baseline	2.27	2.62	0.25	1.61	1.31	2.55	10.557	.000

[a]df = 2,162.
[b]df = 2,161.

score of CDS) at 6 weeks as covariates. The results of the analyses were not essentially affected by these covariates. Post hoc pairwise analysis revealed the disadvantage of haloperidol over olanzapine ($p < .0001$). No significant differences were found when risperidone-treated versus olanzapine-treated subjects and risperidone-treated versus haloperidol-treated subjects were compared. Accordingly, the percentage of patients with treatment-emergent parkinsonism (a total score higher that 3 on the Simpson-Angus at any postbaseline visit, given a total score of 3 or less at baseline) was statistically greater in the haloperidol group (N = 26; 46.4%) when compared to olanzapine (N = 3; 5.5%) and risperidone (N = 15; 24.6%) ($\chi^2 = 24.519$; $p < .001$).

A similar pattern emerged on the BAS. Analyses of variance showed no significant between-treatment differences in akathisia severity at baseline ($F = 0.003$; $p = .997$) (Table 3). The ANOVA showed that baseline-to-end changes were statistically significant among groups of treatment ($F = 4.576$; $p = .012$) (Table 3). The post hoc pairwise analysis revealed that haloperidol-treated patients showed an increase in the severity of akathisia (assessed by BAS total score) when compared to the olanzapine-treated group ($p = .009$). The comparison of risperidone and olanzapine and risperidone and haloperidol did not reveal significant changes over time for akathisia severity. Consistently, a significantly higher number of patients in the haloperidol-treated group (N = 31; 55.4%) experienced treatment-emergent akathisia (BAS global score of 2 or more at any postbaseline visits, given a global score of less that 2 at the baseline visit) when compared to risperidone-treated individuals (N = 16; 26.2%) and patients taking olanzapine (N = 3; 5.5%) ($\chi^2 = 33.882$; $p < .001$).

The means for total AIMS scores did not show any significant increment of abnormal involuntary movement after 6 weeks of treatment with any of the 3 antipsychotics ($F = 2.824$; $p = .063$).

Concomitant medication use. The rates of treatment with concomitant medications were also different among groups. The 6-week data indicate that anticholinergics for extrapyramidal symptoms were prescribed for 74.5% of those receiving haloperidol (N = 41 of 55), 32.8% of those receiving risperidone (N = 19 of 58), and 3.8% of those receiving olanzapine (N = 2 of 52) ($\chi^2 = 57.842$; $p < .0001$).

During the acute phase, there were no statistical differences in the usage of benzodiazepines for anxiety/agitation or extrapyramidal symptoms (N = 19, 34.5% haloperidol; N = 13, 22.4% risperidone; and N = 14, 26.9% olanzapine) ($\chi^2 = 2.10$; $p = .350$) or in the use of hypnotics (N = 9, 16.4% haloperidol; N = 6, 10.3% risperidone; and N = 4, 7.7% olanzapine) ($\chi^2 = 2.093$; $p = .351$) among treatment arms.

Adverse events. The adverse events were evaluated using the UKU (Table 4). Only adverse effects rated as moderate or severe and with a causal relationship to medication of possible or probable were recorded. Those treatment-emergent adverse events that occurred at a rate of at least 10% in either treatment group at 6 weeks are shown in Table 4. Haloperidol-treated patients experienced a statistically significantly greater prevalence of difficulties in concentration, rigidity, hypokinesia, and akathisia. Olanzapine-treated patients experienced a statistically significant increase in body weight (defined by an increase of at least 4 kilograms) (47%; N = 26 of 55) compared to 23% in the risperidone-treated (N = 14 of 61) and 9% in the haloperidol-treated (N = 5 of 56) groups ($\chi^2 = 21.623$; $p < .001$). The olanzapine-treated and haloperidol-treated patients experienced a significant increase in the prevalence of treatment-emergent somnolence compared to risperidone (olanzapine 46%, 25 of 55; haloperidol 46%, 26 of 56; and risperidone 23%, 14 of 61) ($\chi^2 = 8.866$; $p = .012$).

DISCUSSION

There are no studies that have evaluated the effectiveness, tolerability, and safety of atypical (olanzapine and

Table 4. Clinical Adverse Events Reported by 172 Drug-Naive Patients With a First Episode of Psychosis Randomly Assigned to Treatment With Risperidone, Olanzapine, or Haloperidol at 6-Week Evaluation

	Haloperidol (N = 56)		Olanzapine (N = 55)		Risperidone (N = 61)			
Variable	N	%	N	%	N	%	χ^2 (df = 2)	p
Psychic side effect								
Concentration difficulties	8	14.3	2	3.6	2	3.3	…	.044[a]
Asthenia	24	42.9	16	29.1	17	27.9	3.558	.169
Sleepiness/sedation	26	46.4	25	45.5	14	23.0	8.866	.012
Increased duration of sleep	13	23.2	7	12.7	4	6.6	6.848	.033
Neurologic side effect								
Rigidity	8	14.3	0	0.0	3	4.9	…	.005[a]
Hypokinesia	11	19.6	1	1.8	5	8.2	10.200	.006
Tremor	4	7.1	2	3.6	5	8.2	…	.633[a]
Akathisia	13	23.2	3	5.5	9	14.8	7.049	.029
Autonomic side effect								
Increased salivation	10	17.9	2	3.6	9	14.8	5.806	.055
Reduced salivation	7	12.5	7	12.7	3	4.9	2.618	.270
Other side effect								
Weight gain	5	8.9	26	47.3	14	23.0	21.623	< .001
Erectile dysfunction	5	13.9	1	3.0	3	7.9	…	.244[a]
Ejaculatory dysfunction	2	5.6	0	0.0	5	13.2	…	.072[a]
Amenorrhea	2	10.0	0	0.0	2	8.7	…	.549[a]

[a]Fisher exact test.

risperidone) and typical (haloperidol) antipsychotics in the acute treatment of individuals with a first episode of nonaffective psychosis who are representative of an epidemiologic catchment area and who are treated in routine clinical settings. However, results from previous double-blind controlled studies have shown a similar efficacy of conventional and atypical antipsychotics in the acute reduction of symptomatology in patients with a first-episode psychosis. The strengths of our study are as follows: first, we evaluated a large sample of patients with a first episode of psychosis (N = 172) who were representative of a geographical and administrative area; second, the patients were randomly allocated to treatment; third, 98.5% of patients were drug naive; fourth, the rate of retention during the 6 weeks was high (96%); and fifth, it was a non–industry-sponsored trial.

Effectiveness

Our study demonstrates that haloperidol, risperidone, and olanzapine are equally effective for the acute treatment of first episode of psychosis under usual conditions of real clinical practice. The BPRS, SANS, and SAPS scores at the end of 6 weeks and the changes from baseline evaluation were almost identical for these medications. Moreover, our results, by using a more robust measure of effectiveness (defined as a 40% or greater improvement from the total BPRS score), have shown that patients in any of the 3 treatment groups had a similar likelihood of achieving a clinical response during this critical period of the illness. These results are consistent with previous double-blind controlled studies showing that conventional and atypical antipsychotics produced a similar significant reduction in the severity of symptomatology in first-episode schizophrenia and also, overall, an equal likelihood of clinical response.[3–8,33]

Sanger et al.[6] compared the efficacy of olanzapine (N = 59) and haloperidol (N = 24) in a subpopulation of first-episode schizophrenia spectrum individuals in a large international multicenter trail. At endpoint, and by using a similar restricted definition of clinical response, they found a rate of clinical response of 67.2% for the olanzapine-treated group (mean dose = 11.6 mg; SD = 5.9) and 29.2% for haloperidol-treated patients (mean dose = 10.8 mg; SD = 4.8). We suggest that discrepancies found in the clinical response rate for haloperidol-treated patients between the 2 studies (29.2% vs. 57.1%) may be due to the following facts. First, Sanger and colleagues[6] reported a higher mean dose of haloperidol (11.6 mg/day) and also a greater rate of dropouts compared to our study (62.5%). Second, their patients had been previously treated for a considerable period of time. That is, if they considered the late observation as the endpoint in the analysis of clinical response, it seems feasible that their patients were still severely ill when they dropped out of the study. Therefore, these methodological differences may potentially explain the low rate of clinical response to haloperidol. Conversely and consistently with our results, Emsley et al.,[7] in a sample of 183 patients with a first episode of schizophrenia, described response rates of 63% for risperidone and 56% for haloperidol. More recently, Lieberman and colleagues,[8] using low doses of olanzapine and haloperidol as well, found similar rates of response (55% of olanzapine-treated and 46% of haloperidol-treated patients) without statistical differences between both treatments. It is noteworthy that we utilized slightly higher mean doses of haloperidol (5.4 mg

[SD = 1.8]) compared to those double-blind controlled studies showing that even lower doses of haloperidol are also effective in first-episode patients.[3,8,33] In our study, the dropout rate in the haloperidol arm is exceptionally low (less than 2%), and the responder rate (54.8%) in the haloperidol-treated group is similar to those described in previous investigations using slightly lower doses of haloperidol.[8,33]

We also found similar improvements in negative symptoms as measured by the total SANS score in the 3 treatment groups. Our findings do not seem to support the notion that SGAs may have significant advantages when compared to FGAs in reducing the severity of negative symptoms, as it was initially reported in short-term studies in chronic schizophrenic patients.[34–36] Leucht and colleagues[14] stated in a meta-analysis investigation that the effect size was very small for the advantages of risperidone and olanzapine when compared to haloperidol in improving negative symptoms. So, it could be the case that the effect size was too small to be detected in our investigation. The lack of advantages among groups in improving negative symptoms could be biased by secondary negative symptoms (fewer extrapyramidal side effects or advantage in affective symptoms).[37] It would be expected that patients who received FGAs are more likely to develop extrapyramidal symptoms (i.e., akinesia, diminished speech) or high depression that, in turn, may be recorded as higher scores on the SANS (secondary negative symptoms). Given that there were higher treatment-emergent extrapyramidal side effects and anticholinergic usage in the haloperidol group in our study, it could be expected that the results on negative symptoms may be biased in any way by these variables. Although this hypothesis is possible, we believe it unlikely, because the finding that haloperidol was effective in reducing negative symptoms despite higher treatment-emergent extrapyramidal side effects and anticholinergic usage further strengthens our claim of no differences among treatments. Moreover, the results in detail, using as covariates the severity of extrapyramidal and depressive symptoms at 6-week interview, continued revealing similar advantages in negative symptoms in the 3 treatment groups, suggesting there was no bias in any way due to secondary negative symptoms.

Other studies have also suggested the advantage of risperidone[38] and olanzapine[39] in mood-elevating or antidepressant effects. In contrast, we found that the 3 groups of medications have a similar effect in improving depressive symptoms measured by total scores of the HAM-D and CDS in early phases of psychosis.

Side Effects and Concomitant Medications

Given the high scores in scales measuring extrapyramidal symptoms in patients receiving haloperidol, our findings are consistent with the notion that the effectiveness of haloperidol in controlling the acute psychotic symptomatology is associated with higher treatment-emergent extrapyramidal side effects. Similarly, there was also a higher rate of patients who received concomitant medications (biperiden) as treatment for the extrapyramidal signs and symptoms in the haloperidol-treated group. Consistently, previous investigations have also found, even using slightly lower doses of haloperidol, a significantly greater prevalence of emergent extrapyramidal signs and symptoms in patients treated with haloperidol compared to individuals who were treated with olanzapine[8] and risperidone.[33] Lieberman and colleagues[8] reported essentially similar rates of treatment-emergent parkinsonism and akathisia (55% and 51%, respectively) even when they used lower doses of haloperidol (4.4 mg/day). The high rate of parkinsonism and akathisia even with low doses of haloperidol (4 mg/day) had been previously demonstrated in a dose-response study comparing sertindole and haloperidol in a sample of chronically ill patients.[40]

The analysis of the general adverse events experiences using the UKU revealed a higher prevalence of treatment-emergent weight gain in the first 6 weeks of treatment associated with olanzapine (47%) and risperidone (23%) compared to haloperidol (9%). In previous research, olanzapine-treated first-episode patients had also had significantly more weight gain compared to patients treated with haloperidol.[8]

It is of note that a rapid weight gain appears to be more frequent during the first 6 weeks of treatment with olanzapine. Such marked weight gain among young people may also affect tolerability and treatment compliance.[41,42] Despite the real advantage regarding the low rate of emergent extrapyramidal side effects of olanzapine and risperidone, the host of long-term metabolic consequences associated with the use of SGAs is now a major issue in the long-life pharmacologic treatment of psychosis. SGAs are not devoid of adverse side effects that may hazard medication compliance.[17] Based on the notion that FGAs and SGAs seem to have a similar effectiveness to controlling psychopathology, long-term safety concerns have the potential to surpass the prognostic impact of short-term extrapyramidal adverse effects.[12]

Limitations

Our study has several limitations that must be taken into account in the interpretation of these results. First, as a practical clinical trial in our study patients and observer (B.C.-F.) were unblinded with regard to treatment assignment. The fact that the observer knew the antipsychotics prescribed to the patients may influence the interpretation and evaluation of outcomes. Nonetheless, in clinical practice knowledge of medications is part of the ecological validity of outcomes and does not necessarily detract from the robustness of the findings.[18] Moreover, as a

non–industry-funded study, the risk for systematic biased measuring of study outcomes favoring any of the 3 antipsychotics is scarce, and we believe that bias is best controlled by the random assignment of patients to the treatment groups.

Second, likely metabolic changes associated with antipsychotics in the first 6 weeks were not evaluated. Although we are aware of the risks of metabolic side effects associated with the use of antipsychotics, particularly in this population encompassing relatively young individuals,[13] the short time of follow-up of the present study (first 6 weeks) precludes validly and thoroughly exploring the effects of medication on metabolic variables (weight gain, hyperglycemia, glucose levels). So, lengthy follow-up studies are warranted for an accurate investigation of metabolic side effects of antipsychotics in the early phases of the illness and as an aid to clinicians to decide the optimal medication to maximize treatment outcomes and to minimize short-term and long-term safety and adherence concerns.

Third, an additional possible criticism of the study, as mentioned above, is that the haloperidol doses used are somewhat higher than those currently used to treat first-episode individuals in controlled investigations or in specific clinical practice.[43] The mean dose in our study was 5.4 (SD = 1.8) mg/day and was well within treatment guidelines recommended at the time this study was initiated.[7,44–46] Higher doses of haloperidol than currently recommended (no higher than 5 mg/day)[12,47] may produce an unnecessarily high D_2 receptor occupancy, leading to extrapyramidal side effect enhancement and, in turn, to the development of secondary negative symptoms, and this may have affected the outcome of this study. It is noteworthy that we treated a heterogeneous representative sample of drug-naive patients (97% of patients had never received antipsychotics). The sample also included severely ill patients (63.4% of patients were hospitalized) and a high percentage of illicit drug users (47% and 23% of patients were, respectively, cannabis and cocaine users) and so we did not want to hazard the likelihood of undertreatment in this critical period of the illness. Therefore, and associated with a high haloperidol mean dose, an increase in extrapyramidal side effect prevalence and a higher usage of concomitant medications were also observed. It may be speculated that these facts may have implications for poorer compliance and so a greater risk of dropouts. Although this explanation is feasible, we believe it unlikely because there were no differences in the number of patients in each treatment group who were retained in the study. It has been stated that optimal doses of antipsychotics may lie between clinical effectiveness and avoidance of adverse effects and should be established according to the clinical situation. The SGAs have better-defined reference ranges for first-episode psychoses than FGAs.[13]

On the basis of these results, we conclude that risperidone, haloperidol, and olanzapine are equally effective in reducing the psychopathology (positive, negative, and affective symptomatology) during the acute phase of nonaffective psychosis in a representative cohort of first-episode patients who were treated in routine clinical conditions. However, a different profile in side effects and in the need of concomitant medication was found among the different antipsychotics. The FGA haloperidol was associated with a higher rate of acute treatment-emergent extrapyramidal side effects and with a more frequent use of concomitant medications. The SGAs olanzapine and risperidone were associated with a greater potential for weight gain. The impact of short-term and long-term profiles of side effects associated with the early phases of the illness and antipsychotics deserves further follow-up investigations that accurately evaluate clinical, social, and functional outcomes. Appropriately balancing risk and benefits of antipsychotic medications and, consequently, guaranteeing a good adherence to antipsychotic treatment is the real challenge in treating people with a first episode of psychosis.

Drug names: biperiden (Akineton), clonazepam (Klonopin and others), haloperidol (Haldol and others), lithium (Eskalith, Lithobid, and others), olanzapine (Zyprexa), risperidone (Risperdal), and sertraline (Zoloft).

REFERENCES

1. Birchwood M, Todd P, Jackson C. Early intervention in psychosis: the critical period hypothesis. Br J Psychiatry Suppl 1998;172:53–59
2. Lieberman JA. Atypical antipsychotic drugs as a first-line treatment of schizophrenia: rationale and hypothesis. J Clin Psychiatry 1996; 57(suppl 11):68–71
3. Robinson DG, Woerner MG, Alvir JMJ, et al. Predictors of treatment response from the first episode of schizophrenia or schizoaffective disorder. Am J Psychiatry 1999;156:544–549
4. May PR, Tuma AH, Dixon WJ, et al. Schizophrenia: a follow-up study of the results of five forms of treatment. Arch Gen Psychiatry 1981;38: 776–784
5. Sheitman BB, Lee H, Strous R, et al. The evaluation and treatment of first-episode psychoses. Schizophr Bull 1997;23:653–661
6. Sanger TM, Lieberman JA, Tohen M, et al. Olanzapine versus haloperidol treatment in first-episode psychosis. Am J Psychiatry 1999;156: 79–87
7. Emsley RA (Risperidone Working Group). Risperidone in the treatment of first-episode psychotic patients: a double-blind multicenter study. Schizophr Bull 1999;25:721–729
8. Lieberman JA, Tollefson G, Tohen M, et al. Comparative efficacy and safety of atypical and conventional antipsychotic drugs in first-episode psychosis: a randomized, double-blind trial of olanzapine versus haloperidol. Am J Psychiatry 2003;160:1396–1404
9. McEvoy JP, Hogarty GE, Steingard S. Optimal dose of antipsychotics in acute schizophrenia: a controlled study of the antipsychotic threshold and higher haloperidol dose. Arch Gen Psychiatry 1991;48:739–745
10. Chatterjee A, Chakos MH, Koreen A, et al. Prevalence and clinical correlates of extrapyramidal signs and spontaneous dyskinesia in never-medicated schizophrenic patients. Am J Psychiatry 1995;152:1724–1729
11. Basson BR, Kinon BJ, Taylor CC, et al. Factors influencing acute weight change in patients with schizophrenia treated with olanzapine, haloperidol, or risperidone. J Clin Psychiatry 2001;62:231–238
12. Kelly DL, Conley RR, Carpenter WT. First-episode schizophrenia: a focus on pharmacological treatment and safety considerations. Drugs

2005;65:1113–1138
13. Lambert M, Conus P, Lambert T, et al. Pharmacotherapy of first-episode psychosis. Expert Opin Pharmacother 2003;4:1–34
14. Leucht S, Pitschel-Walz G, Abraham D, et al. Efficacy and extrapyramidal side effects of the new antipsychotics olanzapine, quetiapine, risperidone, and sertindole compared to conventional antipsychotics and placebo: a meta-analysis of randomised controlled trials. Schizophr Res 1999;35:51–68
15. Geddes J, Freemantle N, Harrison P, et al. Atypical antipsychotics in the treatment of schizophrenia: a systematic overview and meta-regression analysis. BMJ 2000;321:1371–1376
16. Chakos M, Lieberman J, Hoffman E, et al. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomised trials. Am J Psychiatry 2001;158:518–526
17. Fleischhacker WW, Meise U, Gunther V, et al. Compliance with antipsychotic drug treatment: influence of side effects. Acta Psychiatr Scand Suppl 1994;382:11–15
18. March JS, Silva SG, Compton S, et al. The case for practical clinical trials in psychiatry. Am J Psychiatry 2005;162:836–846
19. Rabinowitz J, Bromet E, Davidson M. Are patients enrolled in first episode psychosis drug trials representative of those treated in routine clinical practice? Schizophr Res 2003;61:149–155
20. Zerhouni E. Medicine: the NIH roadmap. Science 2003;302:63–72
21. Andreasen NC. Scale for the Assessment of Positive Symptoms (SAPS). Iowa City, Ia: University of Iowa; 1984
22. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P). New York, NY: Biometrics Research, New York State Psychiatric Institute; 2001
23. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale. Psychol Rep 1962;10:799–812
24. Guy W, ed. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education, and Welfare publication ADM 76-338. Washington, DC: National Institute of Mental Health; 1976:217–222
25. Andreasen NC. Scale for the Assessment of Negative Symptoms (SANS). Iowa City, Ia: University of Iowa; 1983
26. Miller IW, Bishop S, Norman WH, et al. The modified Hamilton Rating Scale for Depression: reliability and validity. Psychiatry Res 1985;14: 131–142
27. Addington D, Addington J, Malika-Tyndale E. Assessing depression in schizophrenia: The Calgary Depression Scale. Br J Psychiatry Suppl 1993;22:39–44
28. Young RC, Biggs JT, Ziegler VE, et al. A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 1978;133:429–433
29. Lingjarde O, Ahlfors UG, Bech P, et al. The UKU Side Effect Rating Scale: a new comprehensive rating scale for psychotropic drugs and cross-sectional study of side effects in antipsychotic-treated patients. Acta Psychiatr Scand Suppl 1987;334:1–100
30. Simpson GM, Angus JW. A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 1970;212:11–19
31. Guy W, ed. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare Publication (ADM) 76-338. Washington, DC: National Institute of Mental Health; 1976:534–537
32. Barnes TR. A rating scale for drug-induced akathisia. Br J Psychiatry 1989;154:672–676
33. Schooler N, Rabinowitz J, Davidson M, et al. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial. Am J Psychiatry 2005;162:947–953
34. Chouinard G, Jones B, Remington G, et al. A Canadian multicenter placebo-controlled study of fixed doses of risperidone and haloperidol in the treatment of chronic schizophrenic patients. J Clin Psychopharmacol 1993;13:25–40
35. Volavka J, Czobor P, Sheitman, B, et al. Clozapine, olanzapine, risperidone and haloperidol in the treatment of patients with chronic schizophrenia and schizoaffective disorder. Am J Psychiatry 2002;159: 255–262
36. Assessing the effects of atypical antipsychotics on negative symptoms: collaborative working group on clinical trial evaluations. J Clin Psychiatry 1998;59(suppl 12):28–34
37. Kopelowicz A, Zarate R, Tripodis K, et al. Differential efficacy of olanzapine for deficit and non-deficit negative symptoms in schizophrenia. Am J Psychiatry 2000;157:987–993
38. Marder SR, Meibach RC. Risperidone in the treatment of schizophrenia. Am J Psychiatry 1994;151:825–835
39. Tollefson GD, Beasley CM Jr, Tran PV, et al. Olanzapine versus haloperidol in the treatment of schizophrenia, schizoaffective and schizophreniform disorders: results of an international collaborative trial. Am J Psychiatry 1997;154:457–465
40. Zimbroff DL, Kane JM, Tamminga CA, et al. Controlled, dose-response study of sertindole and haloperidol in the treatment of schizophrenia. Am J Psychiatry 1997;154:782–791
41. Perkins DO. Predictors of noncompliance in patients with schizophrenia. J Clin Psychiatry 2002;63:1121–1128
42. Allison DB, Casey DE. Antipsychotic-induced weight gain: a review of the literature. J Clin Psychiatry 2001;62(suppl 7):22–31
43. Oosthuizen P, Emsley RA, Turner J, et al. Determining the optimal doses of haloperidol in first-episode psychosis. J Psychopharmacol 2001;15: 251–255
44. Tauscher J, Kapur S. Choosing the right doses of antipsychotics in schizophrenia: lessons from neuroimaging studies. CNS Drugs 2001; 15:671–678
45. Lehman AF, Steinwachs DM. Translating research into practice: the Schizophrenia Patient Outcomes Research Team (PORT) treatment recommendations. Schizophr Bull 1998;24:1–10
46. Zhang-Wong J, Zipursky RB, et al. Optimal haloperidol dosage in first-episode psychosis. Can J Psychiatry 1999;44:164–167
47. Kane JM, Leucht S, Carpenter D, et al. Expert Consensus Guideline Series: Optimizing Pharmacologic Treatment of Psychotic Disorders: introduction, methods, commentary, and summary. J Clin Psychiatry 2003;64(suppl 12):5–19

