Psychopharmacology
DOI 10.1007/s00213-011-2392-3

ORIGINAL INVESTIGATION

Long-term (3-year) effectiveness of haloperidol, risperidone and olanzapine: results of a randomized, flexible-dose, open-label comparison in first-episode nonaffective psychosis

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Received: 14 April 2011 / Accepted: 17 June 2011

Abstract
Rationale To enhance the effectiveness of antipsychotics in first-episode psychosis is crucial in order to achieve the most favourable prognosis. Difference in effectiveness between antipsychotics is still under debate.
Objective The purpose of this study is to determine the long-term (3-year) effectiveness and efficacy of haloperidol, risperidone and olanzapine in first-episode schizophrenia-spectrum disorders.
Method This is a prospective, randomized, open-label study. Data for the present investigation were obtained from a large epidemiologic and 3-year longitudinal intervention programme of first-episode psychosis. One hundred seventy-four patients were randomly assigned to haloperidol (N=56), olanzapine (N=55), or risperidone (N=63) and followed up for 3 years. The primary effectiveness measure was all-cause of treatment discontinuation. In addition, an analysis based on per-protocol populations was conducted in the analysis for clinical efficacy.
Results The treatment discontinuation rate for any cause differed significantly between treatment groups (χ^2=10.752; p=0.005), with a higher rate in haloperidol than in risperidone and olanzapine. The difference in the discontinuation rate between risperidone and olanzapine showed a tendency towards significance (χ^2=3.022; p=0.082). There was a significant difference in the mean time to all-cause discontinuation between groups (log-rank χ^2=12.657;df=2; p=0.002). There were no significant advantages to any of the three treatments in reducing the psychopathology severity.
Conclusions After 3 years of treatment, a lower effectiveness was observed in haloperidol compared to second-generation antipsychotics (SGAs). The use of SGAs for the treatment of early phases of nonaffective psychosis may enhance the effectiveness of antipsychotics.

Keywords Antipsychotics · Schizophrenia · Treatment · Efficacy · Clinical practice

Electronic supplementary material The online version of this article (doi:10.1007/s00213-011-2392-3) contains supplementary material, which is available to authorized users.

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Introduction

Long-term maintenance of antipsychotic treatments from early phases of the illness is crucial in order to achieve the most favourable prognosis of schizophrenia (Wyatt 1991). An optimal clinical efficacy and good tolerability are important factors for ensuring a successful long-term pharmacological treatment (Lieberman 1996). Clinical

Published online: 07 July 2011

effectiveness is determined by both efficacy and tolerability, and it applies to patients in real-world treatment settings. In first episode of psychosis, similar clinical efficacy has been found between second generation of antipsychotics (SGAs) and low doses of first-generation antipsychotics (FGAs; Crespo-Facorro et al. 2006, 2011; Kahn et al. 2008; Lieberman 1996; Lieberman et al. 2003). The existence of differences in safety and tolerability leads to different treatment discontinuation rates among antipsychotics in the short term. Previous randomized open-label (Crespo-Facorro et al. 2011; Kahn et al. 2008) and double-blind studies (Schooler et al. 2005; Gaebel et al. 2007; Green et al. 2006; McEvoy et al. 2007) have drawn inconclusive results as to the differential effectiveness of SGAs compared to FGAs in first-episode psychosis. Most of these previous studies assessed the effectiveness in the medium term (1 year) (Crespo-Facorro et al. 2011; Kahn et al. 2008; McEvoy et al. 2007; Schooler et al. 2005). However, and due to fact that side effect profile (tolerability) may change over time, studies based on longer follow-up periods comparing the effectiveness of SGAs and FGAs in routine clinical settings may shed new light on the effectiveness of antipsychotics in early phases of schizophrenia.

We set up a 3-year follow-up study to compare the effectiveness and efficacy of SGAs (olanzapine and risperidone) and FGAs (low doses of haloperidol) in first-episode nonaffective psychosis individuals. We hypothesize that SGAs might be clearly more effective than FGAs and that likely disparity in side effect profiles in the long term may determine differences in effectiveness between risperidone and olanzapine.

Method

Study setting and financial support

Data for the present investigation were obtained from a large epidemiological and 3-year longitudinal intervention programme of first-episode psychosis (PAFIP) conducted at the outpatient clinic and the inpatient unit at the University Hospital Marques de Valdecilla, Spain (Pelayo-Teran et al. 2008). Conforming to international standards for research ethics, this programme was approved by the local institutional review board. Patients meeting inclusion criteria and their families provided written informed consent to be included in the PAFIP.

Subjects

From February 2001 to February 2005, all referrals to PAFIP were screened for patients who met the following criteria: (1) 15–60 years, (2) living in the catchment area, (3) experiencing their first episode of psychosis, (4) no prior treatment with antipsychotic medication or, if previously treated, a total life time of adequate antipsychotic treatment of less than 6 weeks and (5) Diagnostic and Statistical Manual of Mental Disorders fourth edition (DSM-IV) criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia or schizoaffective disorder. The diagnoses were confirmed using the Structured Clinical Interview for DSM-IV Axis I Disorders (First et al. 2001) carried out by an experienced psychiatrist 6 months on from the baseline visit.

Study design

This is a prospective, randomized, flexible-dose, open-label study. Patients who agreed to participate were randomly assigned to treatment. At study intake, all patients but three patients were antipsychotic naïve. Patients who were taking antipsychotics at intake underwent a washout period of 5 days before initiating treatment protocol. Dose ranges were 5–20 mg/day olanzapine, 3–6 mg/day risperidone and 3–9 mg/day haloperidol.

The Clinical Global Impression scale (Guy 1976), the Brief Psychiatric Rating Scale total (BPRS) (Overall and Gorham 1962), the Scale for the Assessment of Positive Symptoms (SAPS) (Andreasen 1984), the Scale for the Assessment of Negative symptoms (SANS) (Andreasen 1983), the Hamilton Depression Rating Scale (HDRS; 24 items) (Miller et al. 1985), the Calgary Depression Scale for Schizophrenia (CDSS; Addington et al. 1993) and the Young Mania Rating Scale (YMRS; Young et al. 1978) were used to evaluate clinical symptomatology. To assess adverse events, the Scale of the Udvalg for Kliniske Undersogelser (UKU; Committee of Clinical Trials; Lingjarde et al. 1987), the Simpson–Angus Rating Scale (Simpson and Angus 1970) and the Barnes Akathisia Scale (BAS; Barnes 1989) were utilized. The same trained psychiatrist (BC-F) completed all clinical assessments.

In order to rate functionality, we used the global disability item from the Spanish version of Disability Assessment Schedule (DAS; Janca et al. 1996). Patients were categorized into two groups: good functionality if 1 or lower in the DAS and deficit functionality if 2 or greater in the DAS at 3 years.

Adherence to antipsychotic drugs was assessed by the information obtained from patients and close relatives by the staff (nurse, social worker and psychiatrists) involved in the clinical follow-up. For the present investigation, patients were consensually dichotomized into having a good (defined as patients regularly taking at least 90% of prescribed medication) and a poor adherence (medium or poor compliance).

Our study gave the option to those clinically stable (symptom free at least 12 months) and functionally recovered (at least 6 months of continuous recovery) patients to discontinue use of antipsychotics while continuing to be followed up by study clinicians. Thirteen patients discontinued antipsychotic medication and were carefully monitored during the following 18 months after discontinuation. Eleven out of these 13 patients who had maintained their initially assigned antipsychotic until stopping the treatment and also completed the 3-year assessment were considered as continuing treatment.

Outcome measures

Primary outcome measures: effectiveness

The main outcomes of effectiveness were the percentage of discontinuation of the initially assigned treatment and the mean time to discontinuation. Treatment discontinuation was defined as: (1) the use of a dose below the predefined range including complete discontinuation and (2) the use of another antipsychotic drug (including parenteral antipsychotic drugs) each for more than 14 days over 6 months. Four reasons (1, insufficient efficacy; 2, marked side effects; 3, patient-reported nonadherence; and 4, other reasons) for the discontinuation were recorded. If more than one reason for discontinuation was present, the most important reason according to the above ranking was selected.

Data on antipsychotic treatment (doses, discontinuation and concomitant medications) were registered at baseline, 6 weeks and every 3 months up to the 3-year follow-up interview. Additional outcomes of effectiveness consisted of evaluating functionality and adherence to antipsychotic treatments.

Secondary outcome measures: efficacy and safety

The efficacy outcomes were the mean change from baseline to 3 years in BPRS, SAPS and SANS total scores. Additional analyses included changes from baseline to 3 years in CGS, YMRS, HDRS and CDSS total scores.

Clinical assessments and measurements of side effects were completed at baseline, weekly for the next 4 weeks, at 6 weeks, at 1 year and at 3 years. Detailed analysis of treatment efficacy at 6 weeks and 1 year in this population has been previously reported (Crespo-Facorro et al. 2006, 2011).

Statistical analyses

We assumed a treatment discontinuation rate, at 3-year follow-up, of 70% in patients receiving haloperidol, and 40% in patients receiving SGA drugs (hazard ratio, 0.42). We needed 44 subjects in each group, on the basis of a two-tailed test with α=5% and $1-\beta$=80%.

To ensure group comparability, baseline sociodemographic and clinical characteristics were tested by one-way analysis of variance (ANOVA) or χ^2 test for categorical variables. The proportion of patients who were compliant (good adherence), the frequency of patients who used hypnotics, mood stabilizers, anticholinergics, benzodiazepines or antidepressants, and the Barnes Akathisia and Sympson–Angus scales were categorically analysed between groups by chi-square test.

The primary aim of this study was to test the hypothesis that the three antipsychotic treatments would result in different effectiveness. Kaplan–Meier survival curves and a log-rank test were used to assess time to all-cause medication discontinuation. Percentages of discontinuation rates between groups were examined by means of chi-square tests. For secondary efficacy and safety measures, analysis was by protocol. Differences between groups in the degree of change in clinical scores from baseline were evaluated with analysis of covariance after our having controlled for baseline scores. All patients included in the analysis had the baseline and 3-year assessments. Within-group comparisons were also explored by using the *t* test to analyse baseline to endpoint differences. By using Fisher's exact and chi-square tests evaluated, categorical data were evaluated. All hypotheses were tested by using a two-sided significant level of 0.05.

The Statistical Package for Social Science, version 16.0 was used for statistical analyses. All statistical tests were two-tailed, and although significance was determined at the 0.05 level, this was in the analysis of correlations. No adjustments were made for multiple comparisons.

Results

Description of study cohort

Figure 1 shows the trial profile. Of the 243 individuals who were referred to PAFIP, 184 met inclusion criteria. Of these, 182 patients gave written consent to their participation in the study and were randomly assigned to treatment. Eight of the initial 182 individuals were finally excluded from the final analyses because they did not fully meet inclusion. At the baseline, only 1.7% (*N*=3) of patients reported some prior treatment. The mean self-reported duration of prior treatment was 4 weeks (SD=2; range=2–6). The overall dropout rate at 3 years was small (*N*=37; 21.3%). Demographic and clinical characteristics of patients are shown in Table 1. All (*N*=173), but one Hispanic, were white Caucasian.

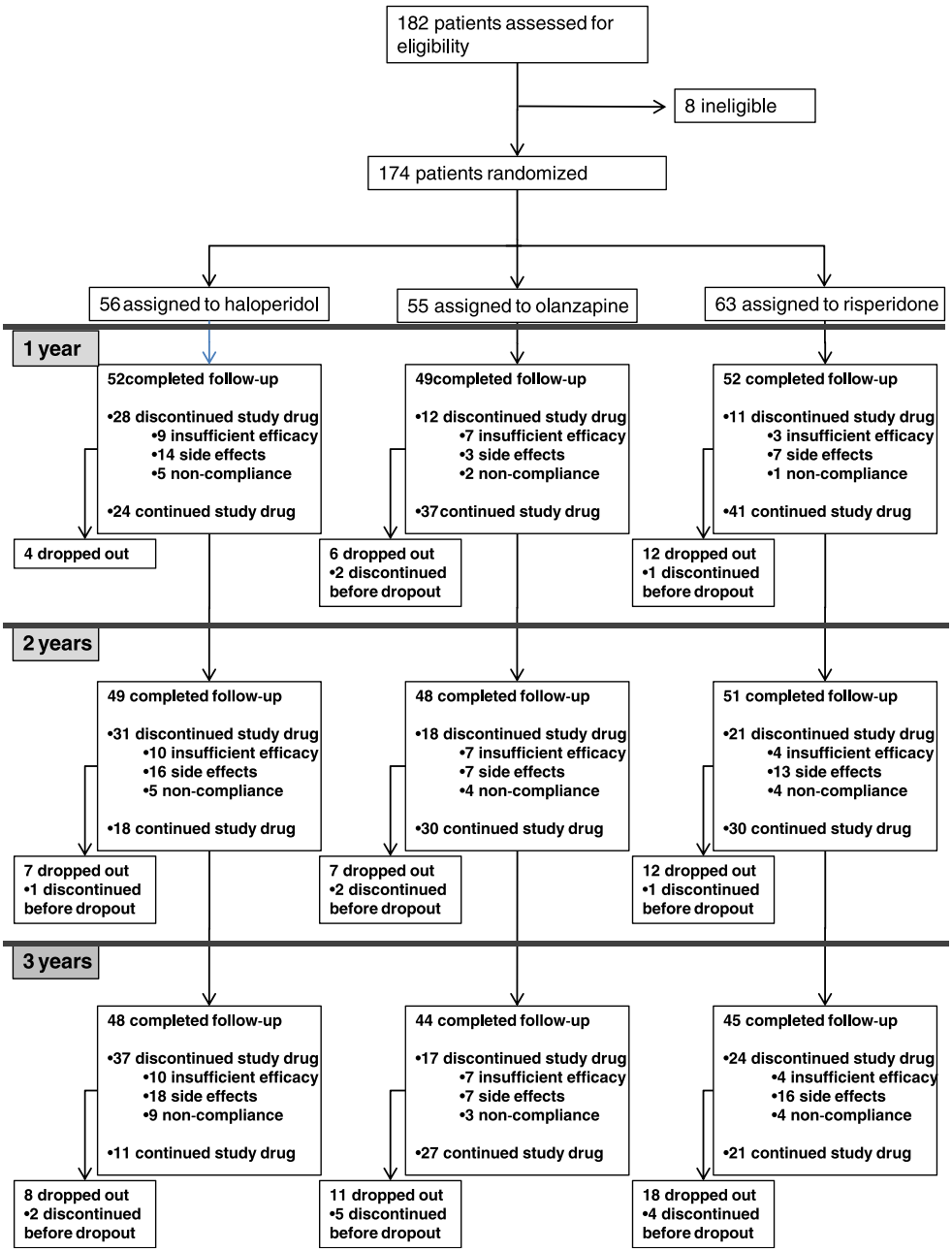

Fig. 1 Flow diagram of subject through the phases of the randomized trial

Mean (SD) and median antipsychotic doses during follow-up were at 3 months: for olanzapine, a mean of 13.3 (4.7) and a median of 15 mg/day; for risperidone, a mean of 3.9 (1.5) and a median of 4 mg/day; and for haloperidol, a mean of 4.9 (2.4) and a median of 4 mg/day; at 1 year: for olanzapine, a mean of 10.2 (3.8) and a median of 10 mg/day; for risperidone, a mean of 3.5 (1.8) and a median of 3 mg/day; and for haloperidol, a mean of 2.9 (1.4) and a median of 2.5 mg/day; at 2 years: for olanzapine, a mean of 11 (4.8) and a median of 10 mg/day; for risperidone, a mean of 3 (1.6) and a median of 3 mg/day; and for haloperidol, a mean of 3.6 (2.5) and a median of 3 mg/day; at 3 years: for olanzapine, a mean of 8.7 (4.6) and a median of 7.5 mg/day; for risperidone, a mean of 2.9 (1.4) and a median of 3 mg/day; and for haloperidol, a mean of 3.2 (1.9) and a median of 2.5 mg/day.

Primary outcome measures

Treatment discontinuation rate and time to discontinuation

The treatment discontinuation rate for any cause differed significantly between treatment groups (χ^2=10.752; p=0.005; Table 2), with a higher rate in haloperidol than in risperidone and olanzapine. The difference in the discontinuation rate

Table 1 Demographic and clinical characteristics of 174 drug-naïve patients with a first episode of psychosis randomly assigned to treatment with risperidone, olanzapine or haloperidol

	Total N=174		Haloperidol N=56		Olanzapine N=55		Risperidone N=63			
Characteristics	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F (df=2,171)	p
Age at admission, year	27.3	7.8	28.3	8.7	27.5	6.9	26.3	7.6	1.02	0.364
Age at psychosis onset, years	26.1	7.2	26.8	7.5	26.5	6.8	25.2	7.2	0.88	0.416
Duration of illness, months	27.8	36.3	32.3	39.7	21.2	33.2	29.5	35.6	1.40	0.249
Duration of psychosis, months	14.4	29.6	17.8	37.2	12.1	29.1	13.4	21.8	0.58	0.561
	N	%	N	%	N	%	N	%	χ^2 (df=2)	p
Gender (male)	108	62.1	36	64.3	33	60.0	39	61.9	0.218	0.897
Education level (elementary)	89	51.1	28	50.0	27	49.1	34	54.0	0.323	0.851
Socioeconomic parents (not/low qualified worker)[a]	104	60.8	36	64.3	32	58.2	36	60.0	0.460	0.795
Urban area (yes)	98	56.3	26	46.4	31	56.4	41	65.1	4.192	0.123
Living with parents (yes)	110	63.2	34	60.7	31	56.4	45	71.4	3.089	0.213
Unmarried (yes)	146	83.9	47	83.9	43	78.2	56	88.9	2.493	0.287
Student (yes)	35	20.1	14	25.0	10	18.2	11	17.5	1.236	0.539
Unemployed (yes)	79	45.4	24	42.9	23	41.8	32	50.8	1.170	0.557
Family psychiatric history (yes)	35	20.1	13	23.2	15	27.3	7	11.1	5.267	0.072
Hospitalization (yes)	109	62.6	41	73.2	35	63.6	33	52.4	5.533	0.063
Cannabis (yes)	82	47.1	25	44.6	26	47.3	31	49.2	0.248	0.883
Alcohol (yes)	96	55.5	34	60.7	25	46.3	37	58.7	2.735	0.255
Other drugs (yes)	47	27.0	13	23.2	17	30.9	17	27.0	0.833	0.659
Diagnosis [b]										
Schizophrenia	107	61.5	42	75.0	29	52.7	36	57.1	6.603	0.037
Other schizophrenia spectrum diagnoses:	67	38.5	14	25.0	26	47.3	27	42.9		
• Schizophreniform disorder	40	23.0	10	17.9	16	29.1	14	22.2		
• Schizoaffective disorder	4	2.3	1	1.8	0	0.0	3	4.8		
• Brief psychotic disorder	9	5.2	1	1.8	4	7.3	4	6.3		
• Unspecified psychotic disorder	14	8.0	2	3.6	6	10.9	6	9.5		

[a] Hollingshead–Redlich scale; analyses were made based on haloperidol=56, olanzapine=55 and risperidone=60

[b] In six of the 174 patients, we could not confirm their DSM-IV criteria initial diagnosis (N=3, schizophrenia; N=2, schizophreniform disorder and N=1, brief psychotic disorder) at 6 months because they had dropped out of the study

between risperidone and olanzapine showed a tendency towards significance (χ^2=3.022; p=0.082; data available under request from the first author). The mean time to all-cause discontinuation was 15.4 months (95% confidence interval (CI), 11.8–18.8) for haloperidol, 23.8 months (95% CI, 20.1–27.4) for olanzapine and 20.7 months (95% CI, 17.2–24) for risperidone. There was a significant difference between the groups (log-rank χ^2=12.657;df=2; p=0.002; see Fig. 2).

Adherence and global functioning

The percentage of good adherence to treatment did not differ significantly between treatments (83.3% haloperidol, 68.2% olanzapine and 78.9% risperidone; χ^2=4.532; df=6; p=0.605) at the 3-year follow-up. The global functional outcome did not differ between treatments with 81.8% haloperidol-treated, 63% olanzapine-treated and 71.4% risperidone-treated patients with a good functionality at the 3-year follow-up (χ^2=1.368; p=0.505).

Secondary outcome measures

Clinical efficacy There were statistically significant differences in the baseline total score of HDRS (F=4.856; p=0.011) between treatment groups. No other significant differences in the severity of symptoms at baseline were found between treatments (see Supplementary material). The univariate ANOVA analysis did not find advantages to any of the three treatments in the reduction of symptomatology at 3 years.

Table 2 Treatment doses and treatment discontinuation by allocated treatment

	Haloperidol, *N*=56			Olanzapine, *N*=55			Risperidone, *N*=63				
	Mean	(SD)	95% CI	Mean	(SD)	95% CI	Mean	(SD)	95% CI		
Mean dose	4.9	1.5	4.4–5.4	12.1	3.7	10.4–13.9	5.6	5.6	3.2–7.9		
Mean dose before discontinuation	5.0	2.3	4.3–5.8	12.9	6.4	9.9–15.9	3.4	1.9	2.6–4.3		
	N	%		*N*	%		*N*	%		χ^2	*p*
Discontinuation for any cause	45	80.4		28	50.9		42	66.7		10.752	0.005
Discontinuation because of insufficient efficacy	10	17.9		7	12.7		4	6.3		3.733	0.155
Discontinuation because of side effect	18	32.1		7	12.7		16	25.4		5.992	0.050
Discontinuation because of noncompliance	9	16.1		3	5.5		4	6.3		4.704	0.095
Discontinuation because of dropout	8	14.3		11	20.0		18	28.6		3.691	0.158

Safety

Extrapyramidal symptoms Treatment-emergent extrapyramidal signs and symptoms were assessed by both baseline-to-end changes and newly emergent categorical changes. No significant differences in the increment of extrapyramidal signs at 3 years were found between treatments (F=2.104; p=0.132; data are available upon request). The percentage of patients with treatment-emergent parkinsonism (a total score higher than 3 on the Simpson–Angus at 3-year assessment, given a total score of 3 or less at baseline) was not statistically different between treatment arms (haloperidol, 9.1%; olanzapine, 0%; and risperidone, 0%; χ^2=4.438; p=0.114), although it could be of clinical relevance.

Haloperidol was associated with a greater increase in akathisia severity (BAS total score) at 3-year assessment (F=4.681; p=0.013). The post hoc pairwise analysis revealed that risperidone-treated patients showed a significant increase in the severity of akathisia when compared to the olanzapine-treated group (F=4.389; p=0.042). Consistently, a significantly higher number in the haloperidol-treated group (18.2%) experienced treatment-emergent akathisia (BAS global score of 2 or more at 3-year evaluation, given a global score of less that 2 at baseline visit) when compared to risperidone-treated (0%) and to olanzapine-treated patients (0%; χ^2=8.668; p=0.013). Severe side effects of antipsychotics which may lead to treatment discontinuation during the follow-up period are not considered in this per-protocol analysis at 3 years.

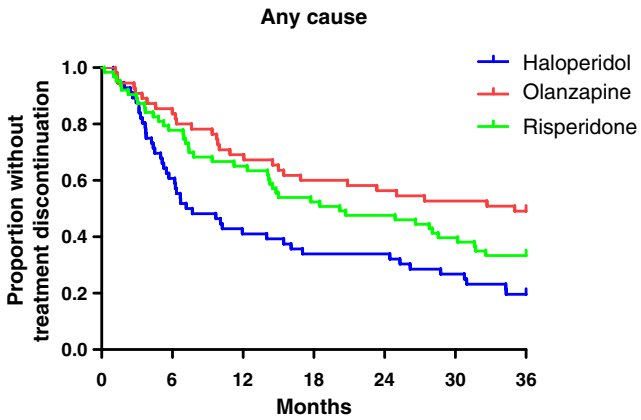

Fig. 2 Time to treatment discontinuation because of any cause

Adverse events The adverse events were evaluated using the UKU side effect rating scale. Those treatment-emergent adverse events that occurred at a rate of at least 5% in either treatment group are shown in Table 3. Only those adverse effects rated as moderate or severe and with a possible causal relationship to medication of possible or probable were recorded. Haloperidol-treated patients experienced a greater prevalence of akathisia (χ^2=9.003; p=0.011). The olanzapine-treated showed a marked increase in the prevalence of treatment-emergent somnolence compared to risperidone and haloperidol (olanzapine, 34.6%; haloperidol, 0%; and risperidone, 10%; χ^2=7.657; p=0.022). There was a higher prevalence of amenorrhea in risperidone-treated female patients (χ^2=6.295; p=0.043). No differences between treatments were found in the frequency of body weight increase (defined by an increase of at least 4 kg) between treatments. The mean increase in body weight over the 3-year period was 8.1 (6.1)kg for haloperidol, 8.8 (7.1)kg for olanzapine and 9.2 (9.2)kg for risperidone. Upcoming publications from our group will describe in detail weight gain and glucose, lipid and peptide

Table 3 Per protocol sample: clinical adverse events reported by patients

	Total N=59		Haloperidol N=11		Olanzapine N=27		Risperidone N=21			
	N	%	N	%	N	%	N	%	χ^2 (df=2)	p
Concentration difficult	3	5.3	1	9.1	2	7.7	0	0.0	1.742	0.419
Asthenia	7	12.3	1	9.1	6	23.1	0	0.0	5.717	0.057
Daytime drowsiness	11	19.3	0	0.0	9	34.6	2	10.0	7.657	0.022
Increased sleep hours	5	8.8	1	9.1	3	11.5	1	5.0	0.606	0.739
Akathisia	4	7.0	3	27.3	0	0.0	1	5.0	9.003	0.011
Sialorrhea	3	5.3	0	0.0	0	0.0	3	15.0	5.858	0.053
Dry mouth	4	7.0	0	0.0	2	7.7	2	10.0	1.121	0.571
Weight gain	12	21.1	1	9.1	7	26.9	4	20.0	1.499	0.473
Amenorrhea[a]	4	17.4	0	0.0	0	0.0	4	40.0	6.295	0.043
Sexual dysfunctions[b]	6	17.6	1	14.3	1	5.9	4	40.0	5.112	0.078

[a] Only females, total N=23; haloperidol=4, olanzapine=9, risperidone=10

[b] Only males, total N=34; haloperidol=7, olanzapine=17, risperidone=10

disturbances at 3 years in this population. Severe side effects of antipsychotics which may lead to treatment discontinuation during the follow-up period are not considered in our per-protocol analysis at 3 years.

Concomitant medication use

The proportion of patients who used anticholinergics, benzodiazepines, hypnotics, antidepressants and mood stabilizers did not differ significantly between treatments at any time (see Supplementary material).

Discussion

In first-episode patients, we found that risperidone and olanzapine have demonstrated higher effectiveness than haloperidol after 3 years of treatment. Consistently, shorter (1 year) follow-up studies had shown a higher rate of discontinuation in patients initially assigned to haloperidol (Crespo-Facorro et al. 2011; Green et al. 2006; Kahn et al. 2008). Nonetheless, not all studies have found a higher effectiveness of SGAs compared to FGA, and a similar effectiveness between risperidone and haloperidol has been also described at both 1-year (Gaebel et al. 2007) and at 2-year (Schooler et al. 2005) follow-ups. The dropout rate from our study was much lower than that seen in previous double-blind or multicenter open-labelled studies, and consequently, the direct comparison with the results from multicenter clinical trials conducted in countries with different systems of healthcare might not be so simple.

Despite methodological differences between studies, we might conclude that SGAs show higher treatment effectiveness compared to FGAs (findings primarily driven by haloperidol). Less clear seems to be the notion that some of the SGAs might be more effective (in terms of treatment discontinuation) than others. Most of the short-term randomized studies have shown similar rates of all-cause treatment discontinuation in first-episode patients treated with different SGAs (Crespo-Facorro et al. 2011; Kahn et al. 2008; McEvoy et al. 2007). In our study, the difference in discontinuation rates at 3 years between olanzapine (50.9%) and risperidone (66.7%) did not reach a statistical significance, but we believe it should be considered as clinically relevant. The direct comparison of discontinuation reasons between olanzapine and risperidone has revealed a trend difference in the discontinuation rate of treatment (χ^2=3.022; df=1; p=0.082) specifically associated with intolerability owing to side effects (χ^2=3.004; df=1; p=0.083). It is of note that our results have revealed similar rates at 1-year (olanzapine, 32.7%; risperidone, 34.9%) and 2-year (olanzapine, 45.5%; risperidone, 52.4%) follow-ups. We suggest that a longer cumulative exposure to risperidone would determine the likelihood of increasing the incidence of disturbing prolactine-related side effects (i.e. sexual side effects; see Table 3) that may lead to an increase in later treatment discontinuations. Contrarily, patients on olanzapine who maintained treatment for the first 2 years are likely to continue taking it for a long time (see Figs. 1 and 2). A higher prevalence of motor side effects might contribute significantly to discontinuation of treatment during early phases (Crespo-Facorro et al. 2011; Kelly et al. 2005), but a higher prevalence of metabolic and endocrine side effects could well influence later discontinuation of treatment.

The overall rate of first-episode patients who discontinued treatment during the first 3 years of treatment

(defined as the percentage of patients who did not maintain their initially assigned antipsychotic and completed the final assessment at 3 years) was 66%. When the completion rate is used as a measure of effectiveness, previous randomized follow-up studies have found even higher rates of antipsychotic discontinuation within a shorter time (1 or 2 years) (Gaebel et al. 2007; Green et al. 2006; Kahn et al. 2008; McEvoy et al. 2007; Schooler et al. 2005).

In the unique previous 3-year follow-up study, Haro et al. (2009), using less stringent criteria to define discontinuation and therefore leading to lower rates of treatment discontinuation, observed that 53.6% of patients did not maintain the initially assigned medication during the 3 years. The fact that patients participating in this non-randomized study were directly recruited by psychiatrists may jeopardize the generalizability of their results and make their findings difficult to compare with our findings obtained from patients involved in an epidemiological and longitudinal intervention programme implemented in routine clinical settings. Our PAFIP clinical programme guarantees the inclusion of most of the first-episode patients in our region and provides continuous clinical attention to patients and their relatives for 3 years after randomized treatment initiation (Pelayo-Teran et al. 2008). Our results seem to provide further support for the notion that running specialized early intervention clinical programmes diminishes the long-term risk of discontinuation among first-episode schizophrenia patients.

The three antipsychotic drugs did not differ from one another in symptoms reduction. Similarly, previous short-term (1 year) controlled studies have also shown that first- and second-generation antipsychotics produced a similar significant reduction in the severity of symptoms in first-episode schizophrenia patients (Crespo-Facorro et al. 2011; Kahn et al. 2008). It is of note that we found similar improvements in negative and depressive symptoms with the three antipsychotics. Consistently, previous longitudinal studies did not observe significant differences between SGAs and FGAs in reducing negative and depressive symptoms (Crespo-Facorro et al. 2011; Gaebel et al. 2007; Green et al. 2006; Kahn et al. 2008; McEvoy et al. 2007). Taking together all these findings, we might conclude that the efficacy of haloperidol for negative and depressive symptoms was similar to that of the SGA drugs, as had been suggested in a systematic review and meta-analysis (Leucht et al. 2009a). It is of note that Leucht et al. (2009b) in another recent meta-analysis described that some SGAs would be somewhat superior (with small to medium effect sizes) to FGAs in improving negative and depressive symptoms.

Our findings have potential limitations. First, as a practical clinical trial, patients and observers (BC-F, IM, RP-I) were not blinded to treatments in our study. The fact that the observers knew the medications prescribed may have involuntarily biased the outcomes. Nevertheless, 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 (March et al. 2005). Second, an additional possible criticism of the study is that the mean doses of antipsychotics used are somewhat higher to those currently used to treat first-episode individuals in controlled investigations or in specific clinics. Optimal doses of antipsychotics were chosen based on clinical efficacy and the presence of adverse effects and were adjusted according to the clinical situation of each individual. The fact that most first-episode cases of nonaffective psychosis which initiate in the epidemiological area were included in our study might be biasing the need for higher doses of antipsychotics, and consequently may have implications for discontinuation rates.

Conclusions

It can be concluded that after 3 years of antipsychotic treatment, (1) a lower effectiveness (measured by percentage of discontinuation of the initially assigned treatment and the mean time to discontinuation) was observed in haloperidol compared to SGAs; (2) for patients who continue with initially assigned treatment, the three antipsychotic drugs showed a similar efficacy for positive, negative and depressive symptoms; and (3) most of the first-episode patients (78.7%) involved in our clinical programme PAFIP kept up an effective treatment. The implementation of specific clinical programmes and the use of SGAs for the treatment of early phases of nonaffective psychosis may enhance the effectiveness of antipsychotic treatments during this crucial phase of the illness.

Acknowledgements We wish to thank the PAFIP researchers who helped with data collection and specially acknowledge Mrs. Gema Pardo for data collection. Finally, we would also like to thank the participants and their families for enrolling in this study.

Conflict of interest disclosures Prof. Vazquez-Barquero and Prof. Crespo-Facorro have received unrestricted research funding from AstraZeneca, Pfizer, Bristol-Myers Squibb and Johnson & Johnson that was deposited into research accounts at the University of Cantabria. Prof. Vazquez-Barquero has received honoraria for his participation as a speaker at educational events from Johnson & Johnson. Prof. Crespo-Facorro has received honoraria for his participation as a speaker at educational events from Pfizer, Bristol-Myers Squibb and Johnson & Johnson and consultant fees from Pfizer. Dr. Mata has received honoraria for his participation as a speaker at educational events from Johnson & Johnson. Dr. Perez-Iglesias has received support to attend conferences from Lilly. Drs. Pelayo-Teran and Valdizan, Mrs. Martinez and Mr. Ortiz report no additional financial or other relationship relevant to the subject of this article.

Funding The present study was carried out at the Hospital Marqués de Valdecilla, University of Cantabria, Santander, Spain under the following grant support: Instituto de Salud Carlos III PI020499, PI050427, PI060507, Plan Nacional de Drogas Research Grant 2005-Orden sco/3246/2004, SENY Fundació Research Grant CI 2005–0308007 and Fundación Marqués de Valdecilla API07/011.
No pharmaceutical company supplied any financial support towards it. The study, designed and directed by B C-F and JL V-B, conformed to international standards for research ethics and was approved by the local institutional review board.

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