Psychopharmacology (2014) 231:357–366
DOI 10.1007/s00213-013-3241-3

ORIGINAL INVESTIGATION

Treatment of first-episode non-affective psychosis: a randomized comparison of aripiprazole, quetiapine and ziprasidone over 1 year

Benedicto Crespo-Facorro · Victor Ortiz-Garcia de la Foz · Ignacio Mata · Rosa Ayesa-Arriola · Paula Suarez-Pinilla · Elsa M. Valdizan · Obdulia Martinez-Garcia · Rocío Pérez-Iglesias

Received: 1 April 2013 / Accepted: 5 August 2013 / Published online: 20 August 2013

Abstract
Rationale Discontinuation of antipsychotic treatment at early phases increases the risk of poor adherence to maintenance drug therapy. Differences among antipsychotics in terms of effectiveness may determine a good adherence to treatment.
Objectives The aim of this study is to compare the clinical effectiveness of aripiprazole, ziprasidone and quetiapine in the treatment of first-episode schizophrenia spectrum disorders at 1 year.
Method From October 2005 to January 2011 a prospective, randomized, open-label study was undertaken. Two hundred two first-episode drug-naïve patients were randomly assigned to aripiprazole (N=78), ziprasidone (N=62), or quetiapine (N=62) and followed up for 1 year. The primary effectiveness measure was all-cause of treatment discontinuation. In addition, an analysis based on intention-to-treat principle was conducted in the analysis for clinical efficacy.
Results The overall dropout rate at 1 year was 13.37 %. The treatment discontinuation rate differed significantly between treatment groups (aripiprazole=43.6 %, ziprasidone=66.1 % and quetiapine=82.3 %) (χ^2=22.545; p<0.001). Insufficient efficacy in the group of quetiapine is the most important reason for differences in discontinuation rates between agents (χ^2=19.436; p<0.001). The mean time to all-cause discontinuation was significantly different between groups (LogRank= 30.732 p<0.001). The profile of extrapyramidal symptoms varies between treatments. Patients on ziprasidone were more likely to be prescribed antidepressants.
Conclusions First episode patients treated with quetiapine have a higher risk of treatment discontinuation at midterm due to insufficient efficacy. Establishing differences between SGAs may help clinicians on prescribing decision for treatment of individuals presenting with first-episode non-affective psychosis.

Keywords Antipsychotic agents · Schizophrenia · Adverse effects · Psychotherapeutic processes

Electronic supplementary material The online version of this article (doi:10.1007/s00213-013-3241-3) contains supplementary material, which is available to authorized users.

B. Crespo-Facorro (✉) · V. Ortiz-Garcia de la Foz · I. Mata · R. Ayesa-Arriola · P. Suarez-Pinilla · O. Martinez-Garcia
University Hospital Marqués de Valdecilla, IFIMAV, University of Cantabria, Cantabria, Spain
e-mail: bcfacorro@humv.es

B. Crespo-Facorro · V. Ortiz-Garcia de la Foz · I. Mata · R. Ayesa-Arriola · E. M. Valdizan · R. Pérez-Iglesias
CIBERSAM, Centro Investigación Biomédica en Red Salud Mental, Madrid, Spain

R. Pérez-Iglesias
Psychosis Studies Department, Institute of Psychiatry, PO63 5th floor, Main building De Crespigny Park, Denmark Hill, London, UK

E. M. Valdizan
Department of Physiology and Pharmacology, University of Cantabria, Cantabria, Spain

E. M. Valdizan
IBBTEC (UC-CSIC-SODERCAN), University of Cantabria, Cantabria, Spain

Introduction

Balancing risks and benefits of antipsychotic agents and subsequently, guaranteeing a good adherence to treatment is the real challenge in the treatment of first-episode psychosis individuals (Crespo-Facorro et al. 2008). Discontinuation of antipsychotic treatment during early phases after a first episode of

psychosis has proven to increase the risk of poor adherence in the long run (Abdel-Baki et al. 2012). Second generation antipsychotics (SGAs) are the first-line drug treatment for individuals suffering from a first-episode schizophrenia (Lieberman 1996). SGAs have shown higher treatment effectiveness compared to first generation antipsychotics (FGAs) (findings primarily driven by haloperidol) in first-episode patients (Crespo-Facorro et al. 2011, 2012; Green et al. 2006; Kahn et al. 2008). The clinical effects and profile of side effects differ between SGAs (Tandon et al. 2008). Less evident seems to be the notion that some of the SGAs might be more effective (in terms of treatment discontinuation) than others (Johnsen and Jorgensen 2008; Leucht et al. 2009). Most of the medium 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). Differences among SGAs in terms of effectiveness have turned out to be a topic of increasing clinical interest, although direct comparisons between the different SGAs are limited in real world clinical practice.

We aimed to evaluate clinical effectiveness at medium term (1 year) of three SGAs (aripiprazole, ziprasidone and quetiapine) widely used to treat individuals with a first episode of non-affective psychosis. We hypothesize that likely disparity in efficacy and side effect profiles may mediate differences in effectiveness. Previous studies from our group investigating the effectiveness of these three SGAs at short term in the same sample have revealed a higher risk of treatment discontinuation in patients initially treated with quetiapine (Crespo-Facorro et al. 2013a, b). Specific short- and mid-term distinctions in clinical efficacy and safety profiles of individual antipsychotics may determine changes in SGAs' effectiveness across time.

Experimental procedures

Study setting and financial support

Data for the present investigation were obtained from an ongoing epidemiological and 3-year longitudinal intervention program 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 program 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 October 2005 to January 2011, 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 lifetime of adequate antipsychotic treatment of less than 6 weeks; (5) DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, or schizoaffective disorder. Patients were excluded for any of the following reasons: (1) meeting DSM-IV criteria for drug dependence, (2) meeting DSM-IV criteria for mental retardation, (3) having a history of neurological disease or head injury. The diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (SCID–I) (First et al. 2001) carried out by an experienced psychiatrist 6 months on from the baseline visit. Our operational definition for a "first episode of psychosis" included individuals with a non-affective psychosis (meeting the inclusion criteria defined above) who have not received previous antipsychotic treatment regardless of the duration of psychosis.

Study design

This is a prospective, randomized, flexible dose, open-label study. We used a simple randomization procedure. A computer-generated randomization list was drawn up by a statistician. At study intake, all patients but eight were antipsychotic naïve. Dose ranges were 5–30 mg/day of aripiprazole, 40–160 mg/day of ziprasidone and 100–600 mg/day of quetiapine. Rapid titration schedule (5 days), until optimal dose was reached, was as a rule used unless severe side effects occur. At the treating physician's discretion, the dose and type of antipsychotic medication could be changed based on clinical efficacy and the profile of side effects during the follow-up period. Antimuscarinic medication, lormetazepam and clonazepam, were permitted for clinical reasons. No antimuscarinic agents were administered prophylactically. Antidepressants and mood stabilizers were permitted if clinically needed.

The severity scale of the Clinical Global Impression (CGI) scale (Guy 1976) the Brief Psychiatric Rating Scale (BPRS) (expanded version of 24 items) (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 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 general adverse event experiences, the scale of the Udvalg for Kliniske Undersogelser (UKU) (Committee of Clinical Trials) (Lingjaerde et al. 1987), the Simpson-Angus Rating Scale (SARS) (Simpson and Angus 1970) and the Barnes Akathisia Scale (BAS) (Barnes 1989) were used to assess side effects. The same trained psychiatrist (BC-F) completed all clinical assessments.

Outcome measures

Primary outcome measures: effectiveness

The main outcome of effectiveness was the percentage of discontinuation of the initially assigned treatment (patients who completed the 1 year follow-up assessment and changed initial antipsychotic) and the mean time to all-cause medication discontinuation (two accepted indexes of medication effectiveness). Four reasons for the discontinuation were recorded: (1) insufficient efficacy; (2) marked side effects; (3) patient reported non-adherence and (4) other causes. If more than one reason for discontinuation was present, the most important reason according to the above ranking was selected. Insufficient efficacy was established at the treating physician's judgment only after at least 3 weeks of treatment.

Secondary outcome measures: efficacy and safety

The efficacy outcomes were the mean change from baseline to 1 year in BPRS, SAPS and SANS total scores. Additional analyses included changes from baseline to 1 year in CGI, YMRS and CDSS total scores. The patients were defined as responders to the optimum dose of antipsychotic at 1 year if a ≥40 % reduction of the BPRS total scores at intake and had a CGI severity score of ≤4. In addition, we also explored the rate of responders if a cutoff of ≥50 % reduction of the BPRS total scores at intake was used.

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 considered. Only those adverse effects rated as moderate or severe and with a possible causal relationship to medication of possible or probable were recorded. Treatment–emergent akathisia (BAS) and extrapyramidal symptoms (SARS) were assessed by both baseline-to-end changes and newly emergent categorical changes. Clinical assessments and measurements of side effects were completed at baseline, 6 weeks, 3 months and 1 year.

Statistical analyses

To ensure group comparability, baseline sociodemographic and clinical characteristics were tested by 1-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, antimuscarinic drugs, benzodiazepines or antidepressants, and the BAS and SARS were categorically analyzed 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 intention-to-treat. In addition, per protocol analyses were performed as well and are available upon request. Differences between groups in the degree of change in clinical scores from baseline were evaluated with analysis of covariance after baseline scores were controlled. All patients included in the analysis had at least the baseline and 1-year assessments. Within-group comparisons were also explored by using the *t* test to analyse baseline to end point 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 19.0, was used for statistical analyses. All hypotheses were tested by using a two-sided significant level of 0.05. No adjustments were made for multiple comparisons.

Results

Description of study cohort

Figure 1 shows the trial profile. Of 224 individuals who were initially randomized to treatments, 22 were finally removed from the data set because it was verified they did not fully meet inclusion criteria or they did not give or remove proper written consent during the first week. Thus, 202 patients who gave written consent to their participation in the study and fulfilled inclusion criteria at 6 months were included in our analyses. The sample size (175) resulted in a sufficient statistical power (95 %) to detect statistically significant differences between groups considering a potential effect size of 0.30 (results based on GPower v 3.1.5). At the baseline, only eight (4.0 %) of patients reported some prior antipsychotic treatment. The mean self-reported duration of prior treatment was 1.5 weeks (SD=1.3; range=0.4–4.0). Before starting on the assigned drug, these subjects underwent a 2–4-day washout period. The overall dropout rate at 1 year was small (N=27; 13.37 %) (16 patients were lost during follow-up (four aripiprazole, three ziprasidone and nine quetiapine); six patients did not show up at 1-year assessment (four aripiprazole and two ziprasidone); four persons committed suicide during 1-year follow-up (one aripiprazole, one ziprasidone and two quetiapine); one sudden death (aripiprazole). All, but ten individuals, were white Caucasian. Demographic and clinical characteristics of patients are shown in Table 1.

In those patients who continued on initially prescribed drug the mean (SD) and median antipsychotic doses at 1 year were: aripiprazole=11.6 (5.8) mg/day and 10.0 mg/day; ziprasidone=61.0 (24.1) mg/day and 60.0 mg/day; and quetiapine=311.4 (177.3) mg/day and 300.0 mg/day.

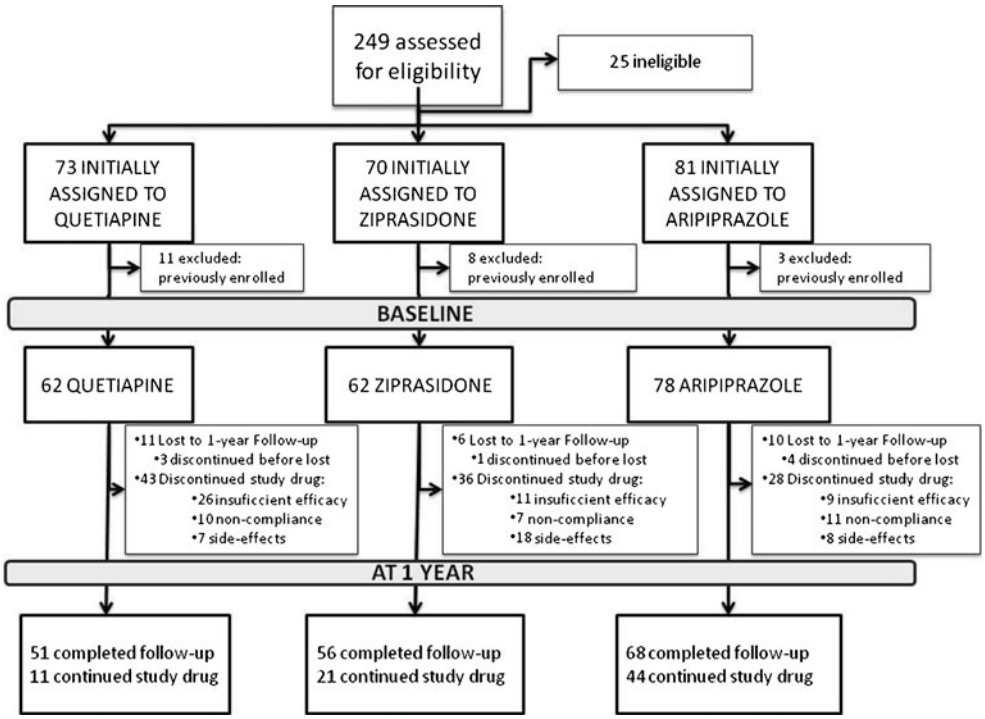

Fig. 1 Flow diagram of subject through the phases of the randomized trial

Primary outcome measures

Treatment discontinuation rate and time to discontinuation

The treatment discontinuation rate for any cause differed significantly between treatment groups (χ^2=22.545; p<0.001) (Table 2). Patients on quetiapine showed a higher rate (82.3 %) of treatment discontinuation than aripiprazole (43.6 %) and ziprasidone (66.1 %) individuals. Insufficient efficacy in the group of quetiapine is the main reason for discontinuation rate differences (χ^2=19.436; p<0.001). The mean time (days) to all-cause discontinuation was 106.71 (95 % CI, 75.19–138.22) for aripiprazole, 129.88 (95 % CI, 95.50–164.25) for ziprasidone and 77.24 (95 % CI, 52.88–101.59) for quetiapine. There was a significant difference between groups in time to discontinuation (Log Rank=30.732; p<0.001) (see Fig. 2). Discontinuation rates because of side effects differed significantly between treatment groups (quetiapine 11.3%, ziprasidone 29 % and aripiprazole 10.3 %; χ^2=10.576; p=0.005).

Secondary outcome measures

Clinical efficacy

There were no statistically significant differences in the severity of symptoms at baseline and at 1 year between treatment groups (Table 3). The univariate ANOVA analysis showed no differences between treatments in reducing symptoms. The rate of responders (≥40 % BPRS and ≤4 CGI) did not differ between groups (aripiprazole, 84.8 %; ziprasidone, 88.9 %; quetiapine, 76.0 %; F=3.271; p=0.195). This difference in the rate of responders between groups was not statistically significant either when the criteria of at least 50 % decrease in total BPRS at baseline was used as cutoff (aripiprazole, 84.8 %; ziprasidone, 87.0 %; quetiapine, 76.0 %; F=2.513; p=0.285). Per-protocol analysis showed, after controlling by SAPS total score at baseline, differences between treatments in reducing positive symptoms (F=5.000; p=0.009). The post hoc pairwise tests revealed a lower effect of quetiapine compared to aripiprazole and ziprasidone (quetiapine vs. ziprasidone, p=0.018; quetiapine vs. aripiprazole, p=0.011; ziprasidone vs. aripiprazole, p=1.000).

Safety

Extrapyramidal symptoms Intention-to-treat analyses have shown no significant differences in the increment of extrapyramidal signs at 1 year (SARS total score) between treatments (F=0.677; p=0.510). The percentage of patients with treatment–emergent parkinsonism (a total score higher than 3 on the SARS at 6-week, 3-month or/and 1-year assessments, given a total score of 3 or less at baseline) was not statistically different between treatment arms (aripiprazole=17.7 %; ziprasidone=19.6 % and quetiapine 14.3 %; χ^2=0.461; p=0.794).

There was not a significant difference between treatments in the severity of akathisia (BAS total score) at 12-month assess-

Table 1 Demographic and clinical characteristics of 202 drug-naïve patients with a first episode of psychosis randomly assigned to treatment with aripiprazole, ziprasidone or quetiapine

	Total (N=202)		Quetiapine (N=62)		Ziprasidone (N=62)		Aripiprazole (N=78)			
Characteristics	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F (df=2)	p
Age at admission (years)	32.0	10.3	31.0	9.2	32.1	10.5	32.6	11.1	0.419	0.658
Age at psychosis onset (years)	30.8	9.9	30.3	9.2	31.1	10.6	30.9	9.9	0.127	0.881
Duration of illness[a] (months)	23.8	45.5	22.1	42.8	16.4	29.4	31.1	56.4	1.840	0.162
Duration of psychosis (months)	14.1	33.1	8.6	12.3	11.9	27.7	20.1	45.5	2.274	0.106
	N	%	N	%	N	%	N	%	χ^2 (df=2)	p
Diagnoses[2]										
Schizophrenia	110	54.5	37	59.7	35	56.5	38	48.7	1.817	0.403
Brief psychotic disorder	30	14.9	9	14.5	6	9.7	15	19.2		
Unspecified psychotic disorder	14	6.9	2	3.2	4	6.5	8	10.3		
Schizophreniform disorder	47	23.3	13	21.0	17	27.4	17	21.8		
Schizoaffective disorder	1	0.5	1	1.6	0	0.0	0	0.0		
Sex (male)	108	53.5	41	66.1	29	46.8	38	48.7	5.819	0.055
Race (white)	192	95.0	58	93.5	94	93.5	76	97.4	1.538	0.464
Education level (elementary)	95	47.3	38	61.3	27	43.5	30	39.0	7.367	0.025
Socioeconomic status of parents (not/less qualified worker)	92	45.8	30	48.4	28	45.2	34	44.2	0.261	0.878
Urban area (yes)	150	74.6	48	77.4	46	74.2	56	72.7	0.408	0.815
Living with parents (yes)	93	46.3	33	53.2	29	46.8	31	40.3	2.332	0.312
Student (yes)	39	19.4	8	12.9	15	24.2	16	20.8	2.678	0.262
Single (yes)	135	67.2	41	66.1	44	71.0	50	64.9	0.610	0.737
Unemployed (yes)	90	44.8	32	51.6	23	37.1	35	45.5	2.665	0.264
Occupational status (yes)	94	46.8	25	40.3	33	53.2	36	46.8	2.073	0.355
Family psychiatric history (yes)	48	23.8	14	22.6	17	27.4	17	21.8	0.672	0.715
Hospital status inpatient (yes)	134	66.3	41	66.1	41	66.1	52	66.7	0.006	0.997
Tobacco use (yes)	119	58.9	39	62.9	33	53.2	47	60.3	1.294	0.524
Cannabis use (yes)	79	39.1	29	46.8	20	32.3	30	38.5	2.765	0.251
Alcohol use (yes)	108	53.5	39	62.9	29	46.8	40	51.3	3.485	0.175
Other drugs (yes)	39	19.4	18	29.0	6	9.7	15	19.5	7.426	0.024

[a] Duration of illness was available on aripiprazole=76, ziprasidone=61 or quetiapine=59

[b] In 18 of the 202 patients, we could not confirm their DSM-IV criteria initial diagnosis (N=9, schizophrenia; N=4, schizophreniform disorder and N=5, brief psychotic disorder) at 6 months because they had dropped out of the study

ment (F=1.705; p=0.185). Although the difference did not reach a significant level, a higher number of individuals in the aripiprazole- (30.6 %) and ziprasidone-treated groups (26.0 %) experienced treatment–emergent akathisia (BAS global score of 2 or more at 6-week, 3-month or/and 1-year evaluations, given a global score of less that 2 at baseline visit) compared to quetiapine-treated subjects (14.0 %) (χ^2=3.910; p=0.142). Per-protocol analysis showed rather similar results (data available upon request).

Adverse events Intention-to-treat analyses of moderate and severe side events that occurred at a rate of at least 5 % in either treatment group are displayed in Table 4. No significant differences between treatments were found. When all adverse events (including also mild events) are considered, no significant differences between treatments were either found (see Table S1).

Concomitant medication use

Intention-to-treat analyses showed that patients on ziprasidone were taking significantly more antidepressants at 1-year assessment compared to those patients on aripiprazole and quetiapine (18.0 % quetiapine; 30.9 % ziprasidone and 11.3 % aripiprazole; χ^2=7.214; p=0.027). No significant differences

Table 2 Treatment doses and treatment discontinuation by allocated treatment

	Total (*N*=76)		Quetiapine (*N*=11)			Ziprasidone (*N*=21)			Aripiprazole (*N*=44)				
			Median	Mean	SD	Median	Mean	SD	Median	Mean	SD		
Dose at baseline			200.0	150.0	59.2	40.0	44.8	12.5	10.0	9.3	1.7		
Dose at 1 year			300.0	311.4	177.3	60.0	61.0	24.1	10.0	11.6	5.8		
Dose at treatment discontinuation[a]: insufficient efficacy			600.0	494.2	139.5	120.0	118.2	38.4	30.0	25.6	6.8		
	N	%		*N*	%		*N*	%		*N*	%	χ^2 (df=2)	*p*
Discontinuation for any cause	126	62.4		51	82.3		41	66.1		34	43.6	22.545	0.000
Discontinuation because of insufficient efficacy	46	22.8		26	41.9		11	17.7		9	11.5	19.436	0.000
Discontinuation because of side effect	33	16.3		7	11.3		18	29.0		8	10.3	10.576	0.005
Discontinuation because of non-compliance	28	13.9		10	16.1		7	11.3		11	14.1	0.614	0.736
Discontinuation because of dropout	19	9.4		8	12.9		5	8.1		6	7.7	1.290	0.525

[a] *N*=26 quetiapine, *N*=11 ziprasidone; *N*=9 aripiprazole

were found between groups in the rate of antimuscarinic agents, benzodiazepines, mood stabilizers and hypnotics use at 1 year (see Table S2).

Discussion

Aripiprazole and ziprasidone have demonstrated significantly higher effectiveness (lower discontinuation rate) than quetiapine in the treatment of first-episode patients at 1 year. Insufficient efficacy in the group of quetiapine is the main reason for discontinuation rate differences between antipsychotics. Intention-to-treat analysis revealed no treatment advantages in reducing the severity of symptomatology between the three SGAs. The profile of motor side effects varies between treatments.

Effectiveness Treatment discontinuation rate during the acute treatment of first-episode patients was significantly greater in patients given quetiapine (82.3 %) mainly due to insufficient efficacy. Higher risk of treatment discontinuation in quetiapine-treated patients has already been described during early phases of treatment (Abdel-Baki et al. 2012). It is of interest that most of the discontinuations in the group of quetiapine were due to inefficacy and occurred at early stages of the treatment (see Fig. 2). The mean time to discontinuation in the quetiapine group was significantly shorter (77.2 days) than in the other two treatment groups (106.71 days in the aripiprazole group and 129.88 days in the ziprasidone group). Effectiveness studies using standard dosage ranges pointed out that quetiapine may be somewhat less effective than some other widely used SGAs (Sparshatt et al. 2011). Our results are consistent with the notion that most of the patients who start quetiapine stop taking it

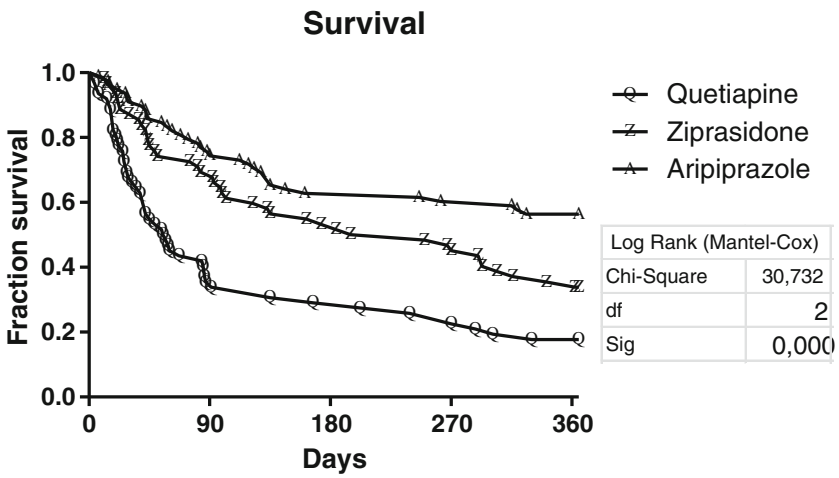

Fig. 2 Kaplan–Meier survival curves for time to treatment discontinuation because any cause

Table 3 Intention-to-treat sample: psychopathological characteristics at baseline, at 1 year and clinical changes during the follow-up period

	Total (N=175)		Quetiapine (N=51)		Ziprasidone (N=56)		Aripiprazole (N=68)			
Variable	Mean	SD	Mean	SD	Mean	SD	Mean	SD	F (df =)	p
CGI total score										
Baseline	6.5	0.6	6.5	0.6	6.4	0.6	6.6	0.6	3.136	0.046
1 year	2.7	1.6	3.1	1.7	2.6	1.5	2.6	1.6	1.715	0.183
1-year change from baseline	−3.8	1.7	−3.4	1.8	−3.8	1.5	−4.1	1.7	2.126	0.123
1-year change from baseline[a]			−3.4	0.2	−3.9	0.2	−4.0	0.2	1.806	0.168
BPRS total score										
Baseline	65.0	12.8	64.7	12.3	61.9	12.6	67.8	12.9	3.292	0.040
1 year	31.2	10.6	31.9	8.9	30.8	11.1	31.1	11.6	0.158	0.854
1-year change from baseline	−33.8	14.9	−32.8	13.2	−31.1	15.8	−36.7	15.2	2.273	0.106
1-year change from baseline[a]			−33.0	1.5	−33.7	1.4	−34.4	1.3	0.231	0.794
SANS total score										
Baseline	4.6	5.4	4.5	5.2	3.8	4.4	5.3	6.3	1.191	0.307
1 year	3.9	4.7	4.2	5.4	3.4	3.7	4.0	4.8	0.408	0.666
1-year change from baseline	−0.7	5.8	−0.3	4.7	−0.4	5.6	−1.3	6.8	0.545	0.581
1-year change from baseline[a]			−0.4	0.6	−1.0	0.6	−0.8	0.6	0.236	0.790
SAPS total score										
Baseline	14.0	4.3	13.9	4.5	13.7	4.2	14.2	4.2	0.199	0.820
1 year	1.3	3.1	1.8	3.0	1.1	3.5	1.0	2.8	1.019	0.363
1-year change from baseline	−12.7	5.0	−12.2	5.1	−12.6	5.5	−13.2	4.5	0.650	0.524
1-year change from baseline[a]			−12.2	0.4	−12.8	0.4	−13.0	0.4	1.051	0.352
CDSS total score										
Baseline	2.7	3.6	2.7	3.2	2.2	3.5	3.2	4.0	1.200	0.304
1 year	0.9	2.1	0.7	1.2	0.9	2.1	1.0	2.6	0.246	0.782
1-year change from baseline	−1.8	4.0	−1.9	3.1	−1.3	3.6	−2.2	4.9	0.907	0.406
1-year change from baseline[a]			−2.0	0.3	−1.8	0.3	−1.8	0.3	0.231	0.794
YMRS total score										
Baseline	11.9	5.3	12.1	6.1	11.7	4.5	11.8	5.4	0.048	0.953
1 year	1.7	2.8	2.0	3.1	1.9	3.2	1.3	2.2	0.988	0.374
1-year change from baseline	−10.2	5.9	−10.1	7.0	−9.9	5.2	−10.6	5.7	0.203	0.817
1-year change from baseline[a]			−9.9	0.4	−10.0	0.4	−10.6	0.3	0.978	0.378

BPRS Brief Psychiatric Rating Scale, *CDSS* Calgary Depression Rating Scale for Schizophrenia, *CGI* Clinical Global Impression, *SANS* Scale for the Assessment of Negative Symptoms, *SAPS* Scale for the Assessment of Positive Symptoms, *YMRS* Young Mania Rating Scale

[a] Controlling by baseline total score

within a few weeks (Komossa et al. 2010). Inadequate and transiently dopamine −2 receptor occupancy with quetiapine may lead to insufficient antipsychotic efficacy (Tauscher-Wisniewski et al. 2002). Nevertheless, previous medium-term randomized studies in first episode showed similar rates of all-cause treatment discontinuation in first-episode patients treated with quetiapine compared to other SGAs (Kahn et al. 2008; McEvoy et al. 2007). Kahn and colleagues (2008) described no difference between quetiapine and ziprasidone in the rate of treatment discontinuation for any cause, although discontinuation because of insufficient efficacy was to some extent higher in quetiapine (40 %) compared with ziprasidone (26 %) at 1 year. Similarly, we found that discontinuation because of insufficient efficacy was higher in quetiapine (41.9 %) compared with ziprasidone (17.7 %) at 1 year. It is of note that Ziprasidone discontinuation seems to occur later on during treatment likely due to the emergence of side effects (29 %). In a sponsored investigation, McEvoy and colleagues (2007) neither observed significant differences between olanzapine, risperidone and quetiapine in clinical efficacy and rate of treatment discontinuation after 1 year.

No differences in depressive symptoms improvement between treatments were observed. Open-label trials had pointed out that quetiapine may be a useful agent in the management

Table 4 Intention-to-treat sample: moderate or severe treatment–emergent adverse events that occurred at a rate of at least 5 % in either treatment group

	Total (*N*=175)		Quetiapine (*N*=51)		Ziprasidone (*N*=56)		Aripiprazole (*N*=68)			
	N	%	*N*	%	*N*	%	*N*	%	χ^2 (df=2)	*p*
Concentration difficulties	12	7.1	2	4.0	5	9.1	5	7.8	1.108	0.575
Asthenia/lassitude/increased fatigability	18	10.7	3	6.0	8	14.5	7	10.9	2.019	0.364
Sleepiness/sedation	16	9.5	4	8.0	5	9.1	7	10.9	0.296	0.862
Depression	7	4.1	1	2.0	3	5.5	3	4.7	0.864	0.649
Increased duration of sleep	15	8.9	3	6.0	8	14.5	4	6.3	3.243	0.198
Increased salivation	6	3.6	4	8.0	0	0.0	2	3.1	4.884	0.087
Constipation	6	3.6	4	8.0	1	1.8	1	1.6	4.112	0.128
Weight gain	34	20.1	10	20.0	10	18.2	14	21.9	0.252	0.882
Amenorrhoea	4	4.9	0	0.0	3	9.7	1	2.9	2.686	0.261
Galactorrhoea	3	3.7	0	0.0	3	9.7	0	0.0	5.123	0.077
Diminished sexual desire	7	4.1	3	6.0	3	5.5	1	1.6	1.746	0.418
Erectile dysfunction	3	3.4	1	3.0	2	8.3	0	0.0	2.809	0.245
Ejaculatory dysfunction	4	4.6	2	6.1	2	8.3	0	0.0	2.370	0.306

of depressive symptoms in individuals with psychosis (Lee et al. 2009; Sajatovic et al. 2002). In previous first-episode studies there were no significant differences between SGAs (including quetiapine) in reducing depressive symptoms after 1 year of treatment (Kahn et al. 2008; McEvoy et al. 2007). No notable changes on negative symptoms were found with any of the three antipsychotics.

Side effects and concomitant medications The differences in the percentage of patients with treatment–emergent parkinsonism (aripiprazole=17.7 %; ziprasidone=19.6 % and quetiapine 14.3 %) and akathisia (aripiprazole: 30.6 %, ziprasidone: 26.0 % and quetiapine: 14.0 %) may be of clinical interest. A higher percentage of extrapiramidal side effects and akathisia in aripiprazole- and ziprasidone-treated individuals during the acute treatment of a first episode has been described (Crespo-Facorro et al. 2013b). A higher incidence of akathisia early after aripiprazole treatment was initiated has been previously reported (Kerwin et al. 2007). Grootens and colleagues (2011) described that significantly more patients on ziprasidone needed antimuscarinic to relieve extrapyramidal symptoms compare to olanzapine-treated patients with recent onset schizophrenia.

No significant differences were found in the frequency of body weight increase between treatments. Intention-to-treat analysis revealed that 20 % of the individuals on quetiapine, 21.9 % on aripiprazole and 18.2 % on ziprasidone showed a rapid body weight gain (Table 4). Komossa and colleagues (2010) described that quetiapine led to more weight increases than ziprasidone. The host of metabolic consequences associated with the use of SGAs is now a major issue in the pharmacological treatment of psychosis. A thorough description and analysis of the effect of the three SGAs on metabolic variables in this sample will be discussed in upcoming articles from our group. In a recent review article, quetiapine showed significantly less use of concomitant antimuscarinic medication than olanzapine, risperidone and ziprasidone (Rummel-Kluge et al. 2012). Interestingly, discontinuation rate due to severe or intolerable side effects in our study was relatively low (16.3 %). We may conclude that, although differences in side effect profile exist, aripiprazole, ziprasidone and quetiapine are devoid of severe adverse side effects that may hazard medication compliance or treatment continuation.

Limitations and strengths Several limitations should be taken into account when interpreting our results. 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. As a non-industry-funded study, the risk for systematic biased measuring study outcomes favouring any of the three SGAs is limited. Second, the mean doses of quetiapine used could be understood as somewhat low to treat first-episode individuals. However, controlled investigations have clearly confirmed that standard dosage range is appropriate in everyday clinical practice with no advantages of high dosage (Johnsen and Jorgensen 2008). Optimal doses of antipsychotics within licensed range were chosen based on clinical efficacy and the presence of adverse effects, and were adjusted according to the clinical situation of each individual.

Conclusions Patients on quetiapine were more likely to discontinue treatment after a first episode of non-affective

psychosis at medium term due to insufficient efficacy compared to aripiprazole and ziprasidone patients. Establishing differences between SGAs may help clinicians on prescribing decision for treatment of individuals presenting with first-episode schizophrenia. Properly balancing risks and benefits of antipsychotic agents and consequently, guaranteeing a good adherence to antipsychotic treatment is the real challenge in the treatment of first-episode psychosis individuals.

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

Conflict of interest disclosures Prof. Crespo-Facorro 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. Crespo-Facorro has received honoraria for his participation as a speaker at educational events from Bristol-Myers Squibb, Astrazeneca, Lundbeck and Johnson & Johnson.

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.

Mr. Valdizan, Mrs. Ayesa, Mrs. Suarez, Mrs. Martinez-Garcia 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 Drugs Research Grant 2005-Orden sco/3246/2004, SENY Fundació Research Grant CI 2005–0308007 and Fundación Marqués de Valdecilla API07/011. Unrestricted educational and research grants from AstraZeneca, Pfizer, Bristol-Myers Squibb and Johnson & Johnson provided support to PAFIP activities. No pharmaceutical industry has participated in the study concept and design, data collection, analysis and interpretation of the results, and drafting the manuscript.

The study, designed and directed by B C-F, conformed to international standards for research ethics and was approved by the local institutional review board.

References

Abdel-Baki A, Ouellet-Plamondon C, Malla A (2012) Pharmacotherapy challenges in patients with first-episode psychosis. J Affect Disord 138(Suppl):S3–S14

Addington D, Addington J, Maticka-Tyndale E (1993) Assessing depression in schizophrenia: the Calgary Depression Scale. Br J Psychiatry (Suppl) 22:39–44

Andreasen NC (1983) Scale for the assessment of negative symptoms (Sans). University of Iowa, Iowa

Andreasen NC (1984) Scale for the assessment of positive symptoms (Saps). University of Iowa, Iowa

Barnes TR (1989) A rating scale for drug-induced akathisia. Br J Psychiatry 154:672–676

Crespo-Facorro B, Perez-Iglesias R, Gonzalez-Blanch C, Mata I (2008) Treatment of the first episode of schizophrenia: an update on pharmacologic and psychological interventions. Curr Psychiatry Rep 10:202–209

Crespo-Facorro B, Perez-Iglesias R, Mata I, Ramirez-Bonilla M, Martinez-Garcia O, Pardo-Garcia G, Caseiro O, Pelayo-Teran JM, Vazquez-Barquero JL (2011) Effectiveness of haloperidol, risperidone and olanzapine in the treatment of first-episode non-affective psychosis: results of a randomized, flexible-dose, open-label 1-year follow-up comparison. J Psychopharmacol 25:744–754

Crespo-Facorro B, Perez-Iglesias R, Mata I, Martinez-Garcia O, Ortiz V, Pelayo-Teran JM, Valdizan E, Vazquez-Barquero JL (2012) Long-term (3-year) effectiveness of haloperidol, risperidone and olanzapine: results of a randomized, flexible-dose, open-label comparison in first-episode nonaffective psychosis. Psychopharmacology (Berl) 219: 225–233

Crespo-Facorro B, Ortiz-García De La Foz V, Mata I, Ayesa-Arriola R, Suarez-Pinilla P, Valdizan E, Vazquez-Barquero JL, Perez-Iglesias R (2013a) Aripiprazole, ziprasidone and quetiapine in the treatment of first-episode nonaffective psychosis: a 12-week randomized, flexible-dose, open-label trial. Schizophr Res 147:373–382

Crespo-Facorro B, Perez-Iglesias R, Mata I, Ortiz-Garcia De La Foz V, Martinez-Garcia O, Valdizan EM, Vazquez-Barquero JL (2013b) Aripiprazole, ziprasidone, and quetiapine in the treatment of first-episode nonaffective psychosis: results of a 6-week, randomized, flexible-dose, open-label comparison. J Clin Psychopharmacol 33:215–220

First MB, Spitzer RL, Gibbon M, William JB (2001) Structured clinical interview for DSM-IV-Tr Axis I disorders-non-patient edition. Biometrics Research Department, New York

Green AI, Lieberman JA, Hamer RM, Glick ID, Gur RE, Kahn RS, McEvoy JP, Perkins DO, Rothschild AJ, Sharma T, Tohen MF, Woolson S, Zipursky RB (2006) Olanzapine and haloperidol in first episode psychosis: two-year data. Schizophr Res 86:234–243

Grootens KP, Van Veelen NM, Peuskens J, Sabbe BG, Thys E, Buitelaar JK, Verkes RJ, Kahn RS (2011) Ziprasidone vs olanzapine in recent-onset schizophrenia and schizoaffective disorder: results of an 8-week double-blind randomized controlled trial. Schizophr Bull 37:352–361

Guy W (1976) Ecdeu assessment manual for psychopharmacology. US Department of Health, Education, and Welfare publication ADM 76338, Washington, DC

Johnsen E, Jorgensen HA (2008) Effectiveness of second generation antipsychotics: a systematic review of randomized trials. BMC Psychiatry 8:31

Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, Gheorghe MD, Rybakowski JK, Galderisi S, Libiger J, Hummer M, Dollfus S, Lopez-Ibor JJ, Hranov LG, Gaebel W, Peuskens J, Lindefors N, Riecher-Rossler A, Grobbee DE (2008) Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet 371:1085–1097

Kerwin R, Millet B, Herman E, Banki CM, Lublin H, Pans M, Hanssens L, L'italien G, Mcquade RD, Beuzen JN (2007) A multicentre, randomized, naturalistic, open-label study between aripiprazole and standard of care in the management of community-treated schizophrenic patients schizophrenia trial of aripiprazole: (STAR) study. Eur Psychiatry 22:433–443

Komossa K, Rummel-Kluge C, Schmid F, Hunger H, Schwarz S, Srisurapanont M, Kissling W, Leucht S (2010) Quetiapine versus other atypical antipsychotics for schizophrenia. Cochrane Database Syst Rev 20;(1):CD006625

Lee KU, Jeon YW, Lee HK, Jun TY (2009) Efficacy and safety of quetiapine for depressive symptoms in patients with schizophrenia. Hum Psychopharmacol 24:447–452

Leucht S, Komossa K, Rummel-Kluge C, Corves C, Hunger H, Schmid F, Asenjo Lobos C, Schwarz S, Davis JM (2009) A meta-analysis of head-to-head comparisons of second-generation antipsychotics in the treatment of schizophrenia. Am J Psychiatry 166:152–163

Lieberman JA (1996) Atypical antipsychotic drugs as a first-line treatment of schizophrenia: a rationale and hypothesis. J Clin Psychiatry 57(Suppl 11):68–71

Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K (1987) The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients. Acta Psychiatr Scand Suppl 334:1–100

McEvoy JP, Lieberman JA, Perkins DO, Hamer RM, Gu H, Lazarus A, Sweitzer D, Olexy C, Weiden P, Strakowski SD (2007) Efficacy and tolerability of olanzapine, quetiapine, and risperidone in the treatment of early psychosis: a randomized, double-blind 52-week comparison. Am J Psychiatry 164:1050–1060

Overall JE, Gorham DR (1962) The brief psychiatric rating scale. Psychol Rep 10:799–812

Pelayo-Teran JM, Perez-Iglesias R, Ramirez-Bonilla M, Gonzalez-Blanch C, Martinez-Garcia O, Pardo-Garcia G, Rodriguez-Sanchez JM, Roiz-Santianez R, Tordesillas-Gutierrez D, Mata I, Vazquez-Barquero JL, Crespo-Facorro B (2008) Epidemiological factors associated with treated incidence of first-episode non-affective psychosis in Cantabria: insights from the clinical programme on early phases of psychosis. Early Interv Psychiatry 2:178–187

Rummel-Kluge C, Komossa K, Schwarz S, Hunger H, Schmid F, Kissling W, Davis JM, Leucht S (2012) Second-generation antipsychotic drugs and extrapyramidal side effects: a systematic review and meta-analysis of head-to-head comparisons. Schizophr Bull 38:167–177

Sajatovic M, Mullen JA, Sweitzer DE (2002) Efficacy of quetiapine and risperidone against depressive symptoms in outpatients with psychosis. J Clin Psychiatry 63:1156–1163

Simpson GM, Angus JW (1970) A rating scale for extrapyramidal side effects. Acta Psychiatr Scand Suppl 212:11–19

Sparshatt A, Taylor D, Patel MX, Kapur S (2011) Relationship between daily dose, plasma concentrations, dopamine receptor occupancy, and clinical response to quetiapine: a review. J Clin Psychiatry 72:1108–1123

Tandon R, Belmaker RH, Gattaz WF, Lopez-Ibor JJ Jr, Okasha A, Singh B, Stein DJ, Olie JP, Fleischhacker WW, Moeller HJ (2008) World Psychiatric Association Pharmacopsychiatry section statement on comparative effectiveness of antipsychotics in the treatment of schizophrenia. Schizophr Res 100:20–38

Tauscher-Wisniewski S, Kapur S, Tauscher J, Jones C, Daskalakis ZJ, Papatheodorou G, Epstein I, Christensen BK, Zipursky RB (2002) Quetiapine: an effective antipsychotic in first-episode schizophrenia despite only transiently high dopamine-2 receptor blockade. J Clin Psychiatry 63:992–997

Young RC, Biggs JT, Ziegler VE, Meyer DA (1978) A rating scale for mania: reliability, validity and sensitivity. Br J Psychiatry 133:429–435