

REGULAR RESEARCH ARTICLE

Long-Term Antipsychotic Effectiveness in First Episode of Psychosis: A 3-Year Follow-Up Randomized Clinical Trial Comparing Aripiprazole, Quetiapine, and Ziprasidone

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Abstract

Background: Different effectiveness profiles among second-generation antipsychotics may be a key point to optimize treatment in patients suffering a first episode of psychosis to affect long-term outcome. The aim of this study was to compare the clinical effectiveness of aripiprazole, ziprasidone, and quetiapine in the treatment of first episode of psychosis at 3-year follow-up.

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 3 years. The primary effectiveness measure was all cause of treatment discontinuation. In addition, an analysis based on the intention-to-treat principle was conducted in the analysis for clinical efficacy.

Results: The overall dropout rate at 3 years reached 19.3%. Treatment discontinuation rates were significantly different among treatment groups (aripiprazole = 73.08%, ziprasidone = 79.03%, and quetiapine = 95.16%) ($\chi^2 = 11.680$; $P = .001$). Statistically significant differences in terms of nonefficacy, nonadherence, and side effects were observed among treatment groups along the 3-year follow-up determining significant differences in time to all-cause discontinuation (log-rank = 32.260; $P = .001$). Significant differences between treatments were found in the categories of sleepiness/sedation ($\chi^2 = 9.617$; $P = .008$) and increased sleep duration ($\chi^2 = 6.192$; $P = .004$). No significant differences were found in the profile of extrapyramidal symptoms. Patients on aripiprazole were more likely to be prescribed benzodiazepines.

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Significance Statement

Preventing relapse after a first episode of psychosis (FEP) is a critical aim to improve long-term outcome of the disease. For this purpose, second-generation antipsychotics (SGAs) seem to be the mainstay of treatment due to their proven superior effectiveness compared with first-generation antipsychotics (FGAs). However, there is scarce information on which to base a prescribing decision after a FEP, because long-term direct comparisons among SGAs are limited in clinical practice. The present paper supplies evidence on the differences in terms of long-term effectiveness among 3 widely used SGAs (aripiprazole, quetiapine, and ziprasidone). In this sense, quetiapine seemed to be the least effective treatment of the trio. Each treatment presented with a different pattern of discontinuation regarding the causes and the time at which discontinuation was more likely to occur. Establishing differences between SGAs regarding risks and benefits of treatments may help clinicians in decisions about prescribing after FEP.

Conclusions: First-episode psychosis patients on quetiapine were more likely to discontinue treatment due to nonefficacy. Identifying different discontinuation patterns may contribute to optimize treatment selection after first episode of psychosis.

Keywords: antipsychotic agents, schizophrenia, first-episode psychosis, effectiveness

Introduction

The early stages after the onset of a first episode of psychosis (FEP) are crucial for the long-term outcome of the disease (Robinson et al., 2005). The course and outcome of schizophrenia are characterized by mainly unexplained heterogeneity (van Os and Kapur, 2009), showing good outcome in <50% of patients (Menezes et al., 2006; Lally et al., 2017). Additionally, three-quarters of all patients who experience a remission from an FEP will have a recurrence of psychotic symptoms within a year of treatment discontinuation, and 95% to 100% of these may experience clinical deterioration (Zipursky et al., 2014). In this sense, prevention of recurrent episodes is likely to be critical to prevent disease progression (Lieberman et al., 2008; Emsley et al., 2013a), and nonadherence to medication seems to represent the highest risk factor (a 4-fold risk) for relapse after an FEP (Alvarez-Jimenez et al., 2012; Caseiro et al., 2012; Emsley et al., 2013b; García et al., 2016). Given that currently it is not possible to discern clearly those individuals that will stay in a benign course from those with a more severe outcome (Leucht et al., 2012), maintenance treatment should be the preferred option even in stable patients after an FEP to remain in recovery (Buchanan et al., 2010; Gaebel et al., 2011). In recent years, this recommendation has been challenged by concerns about the potential antipsychotics long-term adverse outcomes (Wunderink et al., 2013; Gotzsche et al., 2015; Moncrieff, 2015) such as antipsychotic-induced dopamine D2 receptor sensitization, brain volume loss, metabolic syndrome, and other negative effects on physical health (Murray et al., 2016; Goff et al., 2017). These concerns have been minimized by the results of large cohort studies published in recent years indicating that the use of antipsychotics is associated with a lower risk of death or severe health problem when compared with no use (Vanasse et al., 2016; Tiihonen et al., 2017). However, there is still a debate about what is the optimal long-term treatment for patients with an FEP. Although second-generation antipsychotics (SGAs) seem to be the mainstay of treatment to improve the long-term prognosis of people with an FEP, there is scarce information about their differential effectiveness in the long term (Crespo-Facorro et al., 2012). These differences among SGAs in terms of effectiveness might be a key point to optimize the selection of the most appropriate antipsychotic in FEP patients (Shrivastava et al., 2010; San et al., 2012). Nonetheless, direct comparisons between the different SGAs are limited in real world clinical practice (Crespo-Facorro

et al., 2014). All-cause time to treatment discontinuation has been accepted as a proxy measure of effectiveness, incorporating a measure of tolerability (absence of significant side effects) of the medication and clinical efficacy (Lieberman et al., 2005; Kahn et al., 2008). A recent systematic review and pairwise meta-analysis suggested that there is little evidence on which to base drug choice in terms of efficacy in patients presenting with first-episode schizophrenia, so that treatment decisions in this population should be guided by side-effect profiles (Zhu et al., 2017). Previous studies investigating the effectiveness of different SGAs in the short (Crespo-Facorro et al., 2013; Robinson et al., 2015) and mid-term have revealed significant differences in terms of risk of treatment discontinuation SGAs (Lieberman et al., 2005; Robinson et al., 2005; Ciudad et al., 2008; Kahn et al., 2008; Johnsen et al., 2010; Crespo-Facorro et al., 2012; San et al., 2012; Noguera et al., 2013; Zhu et al., 2017). Specific short-mid- and long-term distinctions in clinical efficacy and safety profiles of individual antipsychotics may determine changes in SGAs effectiveness across time. Our study provides a large follow-up period of 3 years, which is an important variable when comparing antipsychotic retention rates (as discontinuation rates generally increase with time) and a sample almost fully integrated by antipsychotic-naïve FEP patients.

Our hypothesis was that the use of aripiprazole, ziprasidone, or quetiapine to treat individuals with an FEP in our study would result in different effectiveness in the long term (3 years). Second, we hypothesized that disparity in efficacy, adherence, and side-effect occurrence may mediate these differences in terms of effectiveness. The aim of this study was to compare directly 3 widely used SGAs and identify differences among them regarding the risks and benefits of each one to guide decisions about prescribing treatment of individuals presenting with FEP.

Experimental procedures

Study Setting

Data for the present investigation were obtained from an ongoing epidemiological and 3-year longitudinal intervention program of first-episode psychosis called Programa de Atención a Fases Iniciales de Psicosis (PAFIP) conducted at the outpatient clinic and inpatient unit of the University Hospital Marqués

de Valdecilla, Spain (Pelayo-Terán 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 prior to their inclusion in the program.

Subjects

From October 2005 to January 2011, all referrals to PAFIP were screened for patients who met the following criteria: (1) 15 to 60 years; (2) living in the catchment area; (3) experiencing their FEP; (4) no prior treatment with antipsychotic medication or, if previously treated, a total lifetime of adequate antipsychotic treatment of <6 weeks; and (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, or (3) having a history of neurological disease or head injury. The diagnoses were confirmed using the Structured Clinical Interview for DSM-IV (First et al., 2002) carried out by an experienced psychiatrist 6 months after the baseline visit. Our operational definition for an FEP included individuals with a nonaffective psychosis (meeting the inclusion criteria defined above) who had not received previous antipsychotic treatment regardless of the duration of psychosis.

Study Design

This was a prospective, randomized, flexible dose, open-label study. We used a simple randomization procedure. An automated randomization list was drawn up. At study intake, all patients but 8 were antipsychotic naïve. Before starting on the assigned drug, these subjects underwent a 2- to 4-day washout period. Mean antipsychotic doses expressed as chlorpromazine equivalents (mg/d) (Woods, 2003) were as follow: quetiapine 100 to 600 mg/d (133.33–800 mg/d of chlorpromazine), ziprasidone 40 to 160 mg/d (66.67–266.67 mg/d of chlorpromazine), and aripiprazole 5 to 30 mg/d (66.67–400 mg/d of chlorpromazine). A rapid titration schedule (5 days), until optimal dose was reached, was used as a rule unless severe side effects occurred. At the treating psychiatrist'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. Anticholinergic medications, lorazepam and clonazepam, were permitted for clinical reasons. No anticholinergic 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, 1989), 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. The scale of the Udvalg for Kliniske Undersogelser (Committee of Clinical Trials) (Lingjærde 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. Clinical assessments and measurements were completed at baseline, at 3 weeks, at 6 weeks, 3 months, 6 months, 12 months, 18 months, 24 months, 30 months, and 36 months. All patients included in the analysis had at least the

baseline and 3-year assessments and were considered for drop-out in those cases in which they did not attend 2 consecutive check-point assessments. The same trained psychiatrist (B.C.-F.) completed all clinical assessments.

Outcome Measures

Primary Outcome Measures: Effectiveness

The main outcome of effectiveness was the treatment discontinuation rate, which is the percentage of all-cause discontinuation of the initially assigned treatment (patients who completed the 3-year follow-up assessment and changed their 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) nonefficacy or insufficient efficacy, (2) significant side effects, (3) nonadherence, and (4) other causes.

Insufficient efficacy was established at the treating physician's judgment only after at least 3 weeks of treatment. Adherence to antipsychotic drugs was assessed by information obtained from patients, close relatives, and the staff (nurses, social workers, and psychiatrists) involved in the 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). If more than one reason for discontinuation was present, the most important reason according to the above ranking was selected.

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 CGI, YMRS, and CDSS total scores. Patients were defined as responders to the optimum dose of antipsychotic if they had a $\geq 50\%$ reduction of BPRS total score and a CGI severity score ≤ 4 after 6 months since the beginning of the treatment. Side effects were evaluated using the Udvalg for Kliniske Undersogelser side effect rating scale. Those treatment-emergent side effects that occurred at a rate of at least 5% in either treatment group at any time during the follow-up period were considered. Only those side effects rated as moderate or severe and with a possible causal relationship to medication were recorded. Treatment-emergent akathisia and extrapyramidal symptoms were assessed using BAS and SARS scales, respectively. Treatment-emergent parkinsonism was defined as a total score > 3 on the SARS at any of the check-point assessments, given a total score of ≤ 3 at baseline.

Statistical Analyses

All data were tested for normality (Kolmogorov-Smirnov test) and equality of variances (Levene test). To ensure group comparability, baseline sociodemographic and clinical characteristics were tested by 1-way ANOVA or Kruskal-Wallis test for continuous variables as necessary or by chi-squared test for qualitative variables.

Kaplan-Meier survival curves and a log-rank test were used to assess time to all-cause medication discontinuation. Concerning these 2 analyses, patients were followed-up from the inclusion in the study until discontinuation of the initial treatment or censoring. Survival time could be censored by the end

of the observation period or by loss to follow-up (patients who dropped out before discontinuation of the initial treatment).

For efficacy and safety measures related to side effects, this research adopted an intention-to-treat analysis paradigm, and patients were followed-up for at least 3 years after their inclusion regardless of whether they had switched their randomly assigned treatment, with the exception of those patients who dropped out of the study and were thus unable to complete the follow-up. In addition, per protocol analyses were performed and are available upon request.

Differences between groups in the degree of change in clinical scores from baseline were evaluated with ANCOVA after baseline scores were controlled. Finally, comparisons of the discontinuation rates and the prevalence of side effects as well as the use of concomitant treatment between the 3 antipsychotics were carried out, performing chi-square tests with Bonferroni correction for multiple comparisons when necessary.

STATA 15.0 was used for statistical analysis. Statistical tests were 2-tailed with a 95% CI.

Results

Of 224 individuals initially randomized to treatments, 22 were finally removed from the dataset because it was verified they did not fully meet inclusion criteria or removed proper written consent during the first week. Thus, the final sample consisted of 202 subjects: 78 patients were randomly assigned to the

aripiprazole group, and 62 patients were randomly assigned to both the quetiapine and ziprasidone groups (Figure 1). At baseline, only 8 (4.0%) 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). The overall dropout rate at 3 years was small (n=39; 19.3%: 12 aripiprazole, 10 ziprasidone, and 17 quetiapine). A total 22 patients dropped out of the follow-up prior to treatment discontinuation and were censored for the survival analysis (9 aripiprazole, 8 quetiapine, and 5 ziprasidone). Four patients committed suicide during the 3-year follow-up (1 aripiprazole, 1 ziprasidone, and 2 quetiapine) and there was one sudden death (aripiprazole; heart attack). All but 10 individuals were white Caucasian. Demographic and clinical characteristics of patients are shown in Table 1.

Primary Outcome Measures

Treatment Discontinuation Rate and Time to Discontinuation

The all-cause treatment discontinuation rate differed significantly between treatment groups ($\chi^2 = 11.680$; $P = .001$) (Table 2). Patients on quetiapine showed a higher (95.16 %) treatment discontinuation rate than patients taking aripiprazole (73.08 %) or ziprasidone (79.03 %). The time (days) until approximately 50% of the patients left their initial treatment due to any cause was 452 days for aripiprazole, 251 days for ziprasidone, and 60 days for quetiapine. There was a significant difference between groups in median time to discontinuation

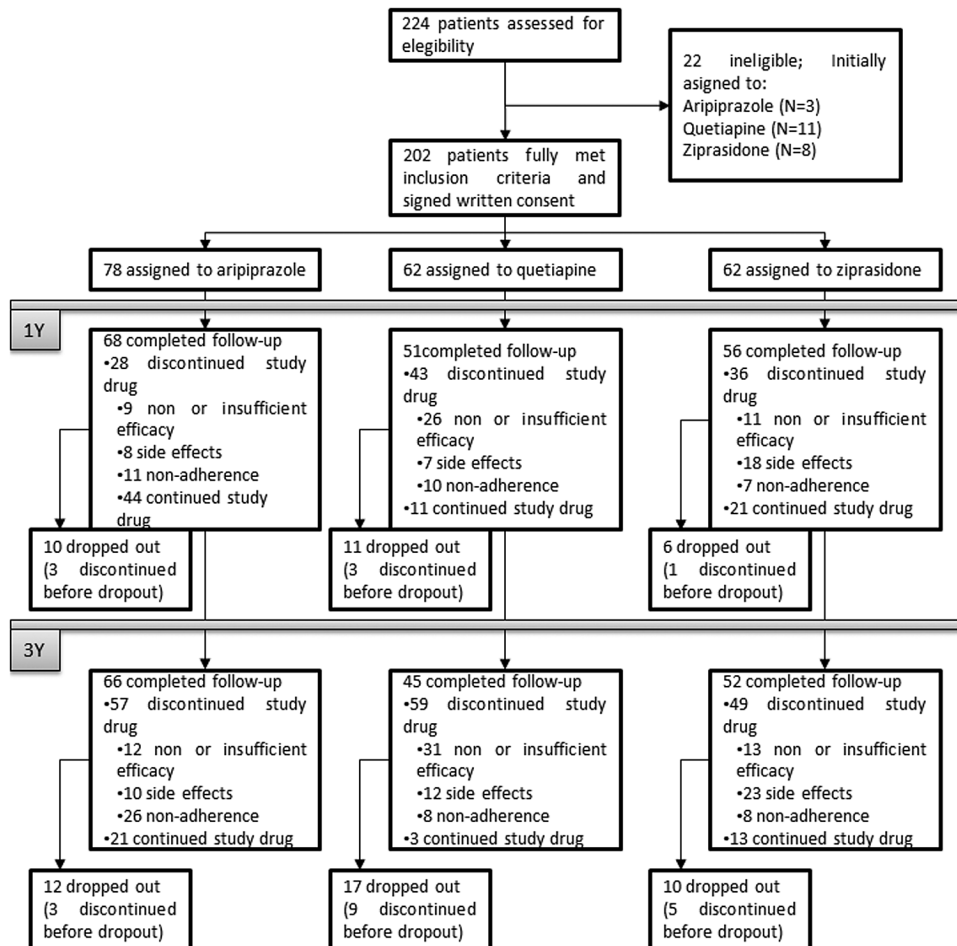


Figure 1. Consort flow diagram of subject through the phases of the randomized trial.

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

Characteristics	Total (n=202)		Quetiapine (n=62)		Ziprasidone (n=62)		Aripiprazole (n=78)		Statistics	P
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
Age at admission (years)	32.0	10.3	31.0	9.2	32.1	10.5	32.6	11.1	F=0.419	.658
Age at psychosis onset (years)	30.8	9.9	30.3	9.2	31.1	10.6	30.9	9.9	F=0.127	.888
Duration of illness ^a (months)	23.8	45.5	22.1	42.8	16.4	29.4	31.1	56.4	z=0.658	.720
Duration of psychosis (months)	2.81	19.0	3.0	11.0	2.25	9.0	2.25	17.1	z=0.226	.893
	N	%	N	%	N	%	N	%	χ^2	P
Schizophrenia diagnosis	113	55.9	38	61.3	36	58.6	39	50.0	1.931	.372
Sex (male)	108	53.5	41	66.1	29	46.8	38	48.7	5.819	.055
Race (white)	192	95.0	58	93.5	94	93.5	76	97.4	1.538	.464
Education level (elementary)	95	47.3	38	61.3	27	43.5	30	39.0	7.367	.025
Socioeconomic status of parents (not/less qualified)	92	45.8	30	48.4	28	45.2	34	44.2	0.261	.878
Urban area (yes)	150	74.6	48	77.4	46	74.2	56	72.7	0.408	.815
Living with parents (yes)	93	46.3	33	53.2	29	46.8	31	40.3	2.332	.312
Student (yes)	39	19.4	8	12.9	15	24.2	16	20.8	2.678	.262
Single (yes)	135	67.2	41	66.1	44	71.0	50	64.9	0.610	.737
Unemployed (yes)	90	44.8	32	51.6	23	37.1	35	45.5	2.665	.264
Occupational status (yes)	94	46.8	25	40.3	33	53.2	36	46.8	2.073	.355
Family psychiatric history (yes)	48	23.8	14	22.6	17	27.4	17	21.8	0.672	.715
Hospital status inpatient (yes)	134	66.3	41	66.1	41	66.1	52	66.7	0.006	.997
Tobacco use (yes)	119	58.9	39	62.9	33	53.2	47	60.3	1.294	.524
Cannabis use (yes)	79	39.1	29	46.8	20	32.3	30	38.5	2.765	.251
Alcohol use (yes)	108	53.5	39	62.9	29	46.8	40	51.3	3.485	.175
Other drugs (yes)	39	19.4	18	29.0	6	9.7	15	19.5	7.426	.024

^aDuration of illness was available on aripiprazole=76, ziprasidone=61, and quetiapine=59.

Table 2. Any-Cause Discontinuation Rate and Discontinuation Rates by Allocated Causes

	Total (n=202)		Aripiprazole (n=62)		Quetiapine (n=62)		Ziprasidone		χ^2	P
	N	%	N	%	N	%	N	%		
Any-cause discontinuation	165	81.68	57	73.08	59	95.16	49	79.03	11.680	.000
No efficacy	56	27.72	12	15.38	31	50.00	13	20.97	22.694	.000
No adherence	46	22.77	26	33.33	12	19.35	8	12.90	8.792	.012
Secondary effects	41	20.29	10	12.82	8	12.90	23	37.10	15.607	.000
Dropout	22	10.89	9	11.53	8	12.90	5	8.06	0.803	.699

(log rank=32.260; $P=.001$) (Figure 2). Log-rank pairwise comparisons between treatment groups showed the following results: aripiprazole vs quetiapine ($\chi^2=28.95$; $P=.000$), ziprasidone vs quetiapine ($\chi^2=14.29$; $P=.000$), and aripiprazole vs ziprasidone ($\chi^2=2.02$; $P=.156$). Consequently, we found statistically significant differences between aripiprazole and quetiapine and between ziprasidone and quetiapine but not between aripiprazole and ziprasidone, where we only found a trend towards nondiscontinuation favoring aripiprazole. Nonefficacy or insufficient efficacy in the quetiapine

group was the main reason for discontinuation rate differences ($\chi^2=22.694$; $P=.000$). Patients under quetiapine treatment were significantly more likely to discontinue due to nonefficacy or insufficient efficacy compared with aripiprazole ($\chi^2=19.450$; $P=.000$) or ziprasidone patients ($\chi^2=11.414$; $P=.000$). No significant differences were found between the aripiprazole and ziprasidone groups in terms of nonefficacy or insufficient efficacy ($\chi^2=0.734$; $P=1.0$). Mean (SD) doses prior to discontinuation due to nonefficacy or insufficient efficacy were: aripiprazole, 15.7 mg (8.6); ziprasidone,

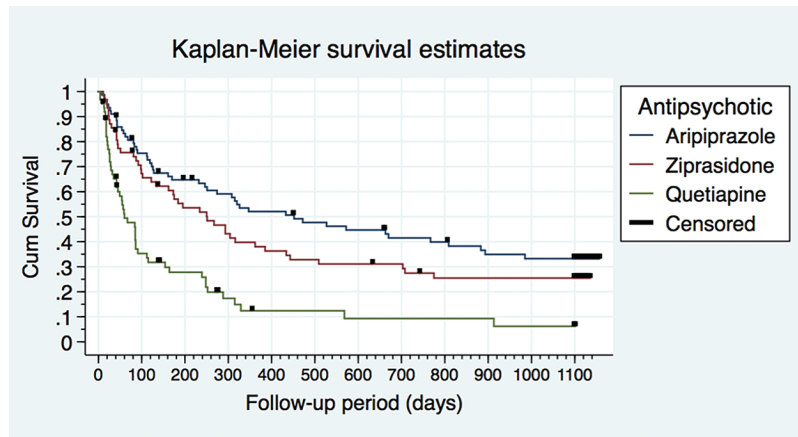


Figure 2. Kaplan-Meier survival graph: All-cause discontinuation.

80.4 mg (40.3); and quetiapine, 490 mg (251.1). Analysis of treatment discontinuation because of side effects showed significant differences between treatment groups (quetiapine 12.9%, ziprasidone 37.1%, and aripiprazole 12.82%; $\chi^2=15.607$; $P=.000$). Patients initially treated with ziprasidone discontinued treatment significantly more frequently than those on aripiprazole ($\chi^2=11.300$; $P=.002$) or quetiapine ($\chi^2=9.677$; $P=.006$) due to side effects. Regarding the direct comparison between quetiapine and aripiprazole, no significant differences were found ($\chi^2=0.000$; $P=1.0$). Finally, there is a remarkable difference in terms of treatment adherence. After intention-to treat analysis, individuals in the aripiprazole group showed worse compliance than those individuals in the ziprasidone group ($\chi^2=8.792$; $P=.012$); however, no differences were found between the aripiprazole and quetiapine groups ($\chi^2=3.413$; $P=.194$) or between the ziprasidone and quetiapine groups ($\chi^2=0.954$; $P=.986$). In those patients who continued taking the initial prescribed drug, mean antipsychotic doses at 3 years, adjusted in chlorpromazine equivalents, were aripiprazole, 216.8 (SD=164.1) mg/d; ziprasidone, 202.2 (SD=136.5) mg/d; and quetiapine, 261.1 (SD=136.5) mg/d, with no significant differences observed ($P=.279$) between treatment groups.

Secondary Outcome Measures

Clinical Efficacy

Intention-to-treat analyses showed that there were no statistically significant differences between treatment groups in the severity of symptoms at baseline and at 3 years except for BPRS ($P=.043$) and CGI ($P=.040$) at baseline (Table 3). Posthoc analyses with Bonferroni correction found statistically significant differences between aripiprazole and ziprasidone in the BPRS ($P=.030$) and CGI scales ($P=.035$) at baseline. ANCOVA analyses showed no differences in the changes of the total scores of the clinical scales between treatments (all $P>.1$) after controlling by baseline measurements except for the CDSS ($P=.026$); Bonferroni correction was significant for the comparison between aripiprazole and quetiapine for the CDSS ($P=.030$).

The rate of responders was also similar between aripiprazole, ziprasidone, and quetiapine (56.28%, 52.84%, 52.11%, respectively; $F=1.25$, $P=.293$). All treatments decreased at least 4 points on the CGI scale from baseline to 3 years (Table 3). Statistically significant differences between treatments were not found ($F=0.41$; $P=.664$).

Safety

Adverse Events

Intention-to-treat analyses of moderate and severe side effects that were frequent (in at least 5% of patients in any of the treatment groups) are displayed in Table 4. Significant differences between treatments were found in the categories of sleepiness/sedation ($\chi^2=9.617$; $P=.008$) and increased sleep duration ($\chi^2=6.192$; $P=.004$). After adjustment by Bonferroni correction, statistically significant differences were only found when comparing aripiprazole and quetiapine for sleepiness/sedation ($P=.007$) and increased sleep duration ($P=.05$). No significant differences between treatments were found after performing per-protocol analysis (data available upon request).

Extrapyramidal Symptoms

Intention-to-treat analyses have shown no significant differences in the increment of extrapyramidal signs at 3 years (SARS total score) between treatments ($F=0.132$; $P=.936$). The percentage of patients with treatment-emergent extrapyramidal symptoms (EPS) was not statistically different between treatment arms (aripiprazole=17.8%; ziprasidone=17.3%, and quetiapine 15.4%; $\chi^2=0.461$; $P=.794$). Per-protocol analysis showed rather similar results (data available upon request). There was no significant difference between treatments in the severity of akathisia (BAS total score) ($F=0.532$; $P=.588$). Although the difference did not reach a significant level, a higher number of individuals in the aripiprazole (22.6%) and ziprasidone groups (32.7%) experienced treatment-emergent akathisia (BAS global score of 2 or more at check-point evaluations, given a global score of <2 at baseline visit) compared with quetiapine-treated subjects (17.8%) ($\chi^2=3.910$; $P=.142$).

Concomitant Medication Use

Intention-to-treat analyses showed no significant differences between antipsychotic treatment groups regarding the use of concomitant medication, except for benzodiazepines ($\chi^2=10.76$, $P=.005$). After adjustment by Bonferroni correction, chi-square tests revealed that benzodiazepine use in the aripiprazole group was significantly higher than in the quetiapine group (92.3% vs 72.6%; $\chi^2=9.791$, $P=.005$). However, there were no statistically significant differences in the use of benzodiazepines between the aripiprazole group and the ziprasidone group (92.3% vs 87.1%; $\chi^2=1.042$, $P=.921$) or between the quetiapine group and the ziprasidone group (72.6% vs 87.1%; $\chi^2=4.06$, $P=.132$).

Table 3. Intention-to-Treat Sample: Psychopathological Characteristics at Baseline and 3 Years and Clinical Changes during the Follow-Up Period

	Total sample		Aripiprazole		Quetiapine		Ziprasidone		F	P
	n=163		n=66		n=45		n=52			
	Mean	SD	Mean	SD	Mean	SD	Mean	SD		
SAPS										
Baseline	14.2	4.3	14.6	4.4	13.9	4.1	13.9	4.3	0.526	.592
3 Years	1.1	2.8	1.0	2.8	1.4	3.0	1.1	2.7	0.314	.731
Change ^a	-13.0	4.8	-13.6	4.7	-12.5	5.3	-12.8	4.6	0.786	.458
Change ^b			-13.2	0.3	-12.7	0.4	-13.1	0.4	0.384	.681
SANS										
Baseline	6.7	6.1	7.5	6.8	6.3	6.0	6.1	5.4	0.906	.406
3 Years	3.6	5.4	3.9	5.7	3.8	5.8	3.1	4.8	0.384	.682
Change ^a	-3.1	7.3	-3.6	8.3	-2.5	5.7	-3.0	7.5	0.287	.751
Change ^b			-2.9	0.7	-2.8	0.8	-3.5	0.7	0.252	.778
BPRS										
Baseline	64.7	12.6	67.7	12.6	63.9	12.0	61.7	12.6	3.524	.032
3 Years	29.9	8.8	29.6	10.0	30.6	9.8	29.1	7.3	0.340	.714
Change ^a	-34.9	13.8	-38.0	15.0	-33.3	13.7	-32.6	12.0	2.712	.069
Change ^b			-35.5	1.1	-34.0	1.3	-35.2	1.3	0.403	.670
CGI										
Baseline	6.5	0.6	6.6	0.6	6.5	0.6	6.3	0.6	3.280	.040
3 Years	2.4	1.6	2.5	1.7	2.5	1.8	2.1	1.4	0.725	.486
Change ^a	-4.2	1.7	-4.2	1.7	-4.1	1.9	-4.2	1.5	0.092	.912
Change ^b			-4.1	0.2	-4.1	0.2	-4.3	0.2	0.410	.664
Positive dimension										
Baseline	7.5	2.4	7.6	2.6	7.6	2.4	7.3	2.3	1.471	.233
3 Years	0.7	1.7	0.5	1.8	1.0	1.9	0.5	1.3	0.424	.655
Change ^a	-6.8	2.8	-7.0	2.8	-6.6	3.0	-6.8	2.6	0.229	.795
Change ^b			-7.0	0.2	-6.5	0.2	-6.9	0.2	1.420	.245
Disorganized dimension										
Baseline	6.7	3.3	7.0	3.2	6.3	3.2	6.6	3.5	0.631	.534
3 Years	0.5	1.6	0.5	1.5	0.4	1.4	0.6	1.8	0.122	.885
Change ^a	-6.2	3.6	-6.5	3.6	-5.9	3.6	-6.0	3.6	0.488	.615
Change ^b			-6.2	0.2	-6.3	0.2	-6.1	0.2	0.112	.894
Negative dimension										
Baseline	4.5	5.4	5.0	6.0	4.3	5.4	3.9	4.7	0.628	.535
3 Years	3.2	4.9	3.5	5.1	3.3	5.1	2.8	4.4	0.326	.722
Change ^a	-1.3	6.4	-1.6	7.2	-1.0	5.0	-1.2	6.5	0.115	.891
Change ^b			-1.1	0.6	-1.1	0.7	-1.6	0.7	0.182	.834
YMRS										
Baseline	11.9	5.0	11.8	5.0	12.3	5.5	11.7	4.6	0.252	.777
3 Years	1.4	3.3	1.0	2.2	1.9	3.6	1.5	4.1	1.073	.345
Change ^a	-10.5	5.4	-10.8	5.0	-10.4	6.8	-10.1	4.7	0.204	.816
Change ^b			-10.9	0.4	-10.0	0.5	-10.3	0.5	0.974	.380
CDSS										
Baseline	2.5	3.5	2.8	3.6	2.7	3.3	2.0	3.5	0.852	.428
3 Years	0.4	1.3	0.7	1.8	0.1	0.3	0.3	0.9	3.753	.026
Change ^a	-2.1	3.7	-2.1	4.1	-2.6	3.3	-1.8	3.5	0.669	.514
Change ^b			-1.8	0.2	-2.5	0.2	-2.3	0.2	3.719	.026

Abbreviations: 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.

^a3-Year change from baseline.

^b3-Year change from baseline after controlling for baseline.

Discussion

In previous studies, aripiprazole and ziprasidone demonstrated significantly higher effectiveness (lower all-cause treatment discontinuation rates and mean time to discontinuation) than quetiapine in the acute treatment of an FEP. This trend was confirmed after a 3-year follow-up. Nonefficacy or insufficient efficacy in the

quetiapine group was the main reason for discontinuation rate differences between antipsychotics. The profile of motor side effects varied between treatments, as did the ability of each group to adhere to treatment. These factors may contribute to additional differences in terms of effectiveness. Instead, intention-to-treat analysis revealed no treatment advantages in reducing the severity of symptomatology (efficacy) between the 3 SGAs.

Table 4. Intention-to-Treat Sample: Moderate or Severe Treatment-Emergent Adverse Effects That Occurred at a Rate of at Least 5% in Either Treatment Group

6-weeks to 3 years	Total		Aripiprazole		Quetiapine		Ziprasidone		χ^2	P
	(n=163)	%	(n=66)	%	(n=45)	%	(n=52)	%		
Concentration difficulties	29	17.8	13	19.7	6	13.3	10	19.2	0.849	.654
Asthenia/increased fatigability	74	45.4	26	39.4	24	53.3	24	46.2	2.115	.347
Sleepiness/sedation	86	52.8	26	39.4	31	68.9	29	55.8	9.617	.008
Memory impairment	7	4.3	3	4.5	1	2.2	3	5.8	0.755	.685
Depression	7	4.3	3	4.5	1	2.2	3	5.8	0.755	.685
Restlessness	7	4.3	3	4.5	1	2.2	3	5.8	0.755	.685
Increased sleep duration	52	31.9	14	21.2	19	42.2	19	36.5	6.192	.045
Rigidity	9	5.5	2	3.0	1	2.2	6	11.5	5.333	.069
Akinesia	46	28.2	23	34.8	8	17.8	15	28.8	3.864	.145
Tremor	14	8.6	9	13.6	2	4.4	3	5.8	3.653	.161
Akathisia	39	23.9	15	22.7	8	17.8	16	30.8	2.325	.313
Increased salivation	29	17.8	11	16.7	9	20.0	9	17.3	0.215	.898
No salivation	22	13.5	5	7.6	8	17.8	9	17.3	3.335	.189
Constipation	19	11.7	7	10.6	7	15.6	5	9.6	0.945	.623
Miction impairment	6	3.7	4	6.1	1	2.2	1	1.9	1.777	.411
Vertigo	7	4.3	3	4.5	0	0.0	4	7.7	3.490	.175
Weight gain	68	41.7	32	48.5	20	44.4	16	30.8	3.944	.139
Diminished sexual desire	16	9.8	6	9.1	6	13.3	4	7.7	0.933	.627
Orgasmic dysfunction	6	3.7	1	1.5	2	4.4	3	5.8	1.587	.452
Amenorrhea	12	14.8	5	14.3	0	0.0	7	23.3	4.515	.105
Galactorrhea	2	2.5	0	0.0	0	0.0	2	6.7	3.486	.175
Erectile dysfunction	14	17.1	2	6.5	7	24.1	5	22.7	3.989	.136
Ejaculatory dysfunction	13	15.9	2	6.5	6	20.7	5	22.7	3.342	.188

Effectiveness

An impressive 80.69 % of the initial sample completed follow-up. The overall treatment discontinuation rate (the cumulative percentage of discontinuation considering the 3 arms of the study) reached 81.7% by 3 years, which is in line with other medium and long-term (52 weeks or more) follow-up studies (Lieberman et al., 2005; McEvoy et al., 2007; Kahn et al., 2008; Mullins et al., 2008; Johnsen et al., 2010; Crespo-Facorro et al., 2012, 2014; San et al., 2012; Noguera et al., 2013). Interestingly, more than three-quarters of the patients who discontinued treatment did so during the first year of follow-up (76.4% by the end of year 1), in agreement with the studies mentioned previously. Such a high all-cause discontinuation rate represents a major issue, considering that adherence to maintenance treatment is the primary aim in FEP patients (San et al., 2012) after remission in order to prevent relapse. The all-cause treatment discontinuation rate in our sample was significantly greater in the quetiapine group, mainly due to nonefficacy or insufficient efficacy. Higher risk of all-cause treatment discontinuation in quetiapine patients had already been described during early phases of treatment (Ciudad et al., 2008; Crespo-Facorro et al., 2014). The median time to all-cause discontinuation in the quetiapine group was significantly shorter (60 days) than in the other 2 treatment groups: 452 days in the aripiprazole group and 251 days in the ziprasidone group. Despite no significant differences between aripiprazole and ziprasidone, there is a clear trend favoring aripiprazole, as can be observed on the K-M survival graph. Both aripiprazole and ziprasidone showed statistically significant superiority over quetiapine regarding median time to all-cause treatment discontinuation. We found that discontinuation because of nonefficacy or insufficient efficacy was higher in quetiapine (50.0%) compared with aripiprazole

(15.38%) and ziprasidone (20.97%). Effectiveness studies using standard dosage ranges pointed out that quetiapine may be less effective than some other widely used SGAs (Ciudad et al., 2008; Asmal et al., 2013; Leucht et al., 2013; Tiihonen, 2016) and FGAs (Vanasse et al., 2016). Regarding the latter study, the authors also warned about a higher risk for health events related to quetiapine. Our results are consistent with the notion that most of the patients who start quetiapine stop taking it within a few weeks (Asmal et al., 2013). Inadequate and transient dopamine-2 receptor occupancy has been proposed as a possible mechanism underlying quetiapine lack of efficacy. On the other hand, its weak dopamine antagonism allows low maximal occupancy values and relatively little variability in occupancy values, suggesting that high doses of this antipsychotic are not likely to exceed thresholds of more than 80% occupancy, indicative for D2-receptor-mediated side effects (Lako et al., 2013). This supports the idea that higher doses may be tolerable and more efficient (McEvoy et al., 2007). We did not find significant differences between groups concerning treatment dosage adjusted by chlorpromazine equivalents prior to discontinuation due to nonefficacy or insufficient efficacy. The quetiapine group presented with a higher relative dosage compared with the other groups. According to other reports (Tiihonen et al., 2017), it is difficult to discern whether the poorer performance of quetiapine is due to the product itself or to nonoptimal dosage. It is of note that ziprasidone and aripiprazole all-cause discontinuations seem to occur later during treatment, likely due to the emergence of side effects (37.1% in ziprasidone group) and nonadherence (33.3% in aripiprazole group), respectively. Actually, most all-cause discontinuations in the ziprasidone sample due to secondary effects (65.2%) took place between 6 and 18 months of follow-up. Finally, most aripiprazole discontinuations were due to nonadherence (53.8%) and accumulated

between the second and third years of follow-up. In this sense, aripiprazole seems to be the most effective and tolerable of the trio. The increase in discontinuations due to nonadherence observed during the last year of follow-up in this group might be explained by a natural decrease in the acceptability of treatment mediated by long-term exposure to treatment (Lieberman et al., 2005). Improvements in educational and other prophylactic measures like the use of long-acting injectable formulations (Jann and Penzak, 2018) may be of interest to deal with this preventable issue.

Efficacy

Our first-episode patients showed a decrease in total BPRS, SAPS, SANS, and CGI scores during the 3-year follow-up. The finding of no significant differences between treatment groups regarding the decrease in these clinical efficacy scales and responder rates agrees with previous reports (McEvoy et al., 2007; San et al., 2012). Remarkably, one-half of quetiapine discontinuations were due to nonefficacy or insufficient efficacy. The absence of differences observed in efficacy measures at 3 years may be attributable to the efficacy of the subsequent antipsychotic employed after initial treatment discontinuation. Differences in depressive symptom improvement between quetiapine and aripiprazole were observed, favoring the quetiapine group. Open-label trials had pointed out that quetiapine may be a useful agent in the management of depressive symptoms in individuals with psychosis (Samara et al., 2015). Quetiapine is acknowledged as a first-line treatment even in monotherapy in affective-psychoses (Lindström et al., 2017), but in several previous first-episode nonaffective psychoses studies, no significant differences between SGAs (including quetiapine) had been found in reducing depressive symptoms after mid-term follow-up (McEvoy et al., 2007; Kahn et al., 2008; Crespo-Facorro et al., 2014). No notable changes on negative symptoms were found with any of the 3 antipsychotics.

Side Effects and Concomitant Medications

The differences in the percentage of patients with treatment-emergent parkinsonism though, nonstatistically significant, may be of clinical interest. A higher percentage of extrapyramidal side effects and akathisia (Juncal-Ruiz et al., 2017) in aripiprazole and ziprasidone-treated individuals during the acute treatment of a first episode has been described. A higher incidence of akathisia early after aripiprazole and ziprasidone treatment was initiated has also been previously reported (Kerwin et al., 2007). This circumstance may partially explain that significantly more patients on aripiprazole needed benzodiazepines to relieve akathisia in our sample. In agreement with previous reports (Lee et al., 2011; Vázquez-Bourgon et al., 2018), no significant differences were found in the frequency of body weight increase between treatments, but a uniform trend to weight increase was appreciated with all of them. Intention-to-treat analysis revealed that 44.4% of the individuals on quetiapine, 48.5% on aripiprazole, and 30.8% on ziprasidone showed a rapid body weight gain (Table 4). Interestingly, the percentage of discontinuation due to severe or intolerable side effects in our study was relatively low (20.9 %) but significant in the case of ziprasidone, because it was its main cause of discontinuation (37.1%). Sleepiness/sedation was the most prevalent reported secondary effect for discontinuation in the case of ziprasidone

($n=8$; 34.7%) despite low doses prior to discontinuation due to secondary effects (58.5 mg [SD=34.3]).

Limitations and Strengths

Several limitations should be considered when interpreting our results. First, as a practical clinical trial, patients and observers (B.C.-F.) 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 favoring any of the 3 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 should be appropriate in everyday clinical practice (Johnsen and Jörgensen, 2008). Optimal doses of antipsychotics within the licensed range were chosen based on clinical efficacy and the presence of side effects and were adjusted according to the clinical situation of each patient. Treatment compliance measures were collected from self-report and close observers (family members and social assistants) but not from antipsychotic blood levels. This could have an impact in the accuracy of discontinuation measures due to noncompliance. On the other hand, this is one of the longest effectiveness studies regarding to follow-up (3 years). It was performed on a well-characterized and homogeneous sample, because most of patients (96%) were antipsychotic naïve prior to their inclusion.

Conclusions

Patients on quetiapine were more likely to discontinue treatment after an FEP globally and specifically at short and medium term due to nonefficacy or insufficient efficacy compared with aripiprazole and ziprasidone patients. Ziprasidone patients showed a greater tendency to discontinuation subordinated to persistent side effects in the mid-term. Finally, the majority of aripiprazole patients (the group with the longer time prior to discontinuation) who quit treatment did so in the last phase of follow-up (most of them reporting non-adherence). In summary, guaranteeing good adherence to effective antipsychotic treatment is one of the main challenges in the treatment of FEP individuals to prevent a malignant course of the disease. Establishing differences between SGAs regarding to risks and benefits of treatments and identifying different discontinuation patterns may contribute to optimize treatment selection after an FEP.

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