

## REGULAR RESEARCH ARTICLE

# Aripiprazole vs Risperidone Head-to-Head Effectiveness in First-Episode Non-Affective-Psychosis: A 3-Month Randomized, Flexible-Dose, Open-Label Clinical Trial

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## Abstract

**Background:** Antipsychotic choice for the acute phase of a first episode of psychosis (FEP) is of the utmost importance since it may influence long-term outcome. However, head-to-head comparisons between second-generation antipsychotics remain scarce. The aim of this study was to compare the effectiveness in the short term of aripiprazole and risperidone after FEP outbreak.

**Methods:** From February 2011 to October 2018, a prospective, randomized, open-label study was undertaken. Two hundred-sixty-six first-episode drug-naïve patients were randomly assigned to aripiprazole (n=136) or risperidone (n=130) and followed-up for 12 weeks. The primary effectiveness measure was all-cause treatment discontinuation. In addition, an analysis based on intention-to-treat principle was conducted to assess clinical efficacy.

**Results:** The overall dropout rate at 12 weeks was small (6.39%). Effectiveness measures were similar between treatment arms as treatment discontinuation rates ( $\chi^2=0.409$ ;  $P=.522$ ), and mean time to all-cause discontinuation (log rank  $\chi^2=-1.009$ ;  $P=.316$ ) showed no statistically significant differences. Despite no statistically significant differences between groups

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## Significance Statement

Antipsychotics are the first-line pharmacological treatment in patients suffering from a first episode of psychosis (FEP). However, their value transcends the acute phase, since they may influence the long-term functional and clinical outcomes for these patients. Thus, the early stages after a FEP represent a window of opportunity during which the optimal antipsychotic treatment choice can positively influence long-term outcomes. In this sense, our paper supplies evidence on the differences regarding effectiveness, efficacy, and side effects of 2 of the most widely used antipsychotics (aripiprazole and risperidone) for the short-term-phase treatment of a FEP. This study was carried out in a well-characterized and homogeneous sample of medication-naïve patients suffering from a FEP. This research, including 266 patients, represents the largest antipsychotic naïve short-term phase FEP effectiveness study comparing head-to-head aripiprazole vs risperidone, and it is the second randomized clinical trial comparing these drugs for FEP treatment reaching this follow-up length.

regarding clinical efficacy, aripiprazole required higher chlorpromazine equivalent dosage ( $\chi^2=2.160$ ;  $P=.032$ ) and extended mean time ( $W=8183.5$ ;  $P=.008$ ) to reach clinical response. Sex-related adverse events and rigidity were more frequent in the risperidone group, whereas sialorrhea was on the aripiprazole group.

**Conclusions:** No differences regarding effectiveness were found between aripiprazole and risperidone for the short-phase treatment of FEP. Despite the importance of efficacy during this phase, differences in side effect profiles and patient's preferences are essential factors that may lead clinical decisions for these patients.

**Clinicaltrials.gov:** NCT02532491. Effectiveness of Second-Generation Antipsychotics in First Episode Psychosis Patients: 1-year Follow-up (PAFIP3\_1Y).

**Keywords:** Antipsychotics, first-episode-psychosis, schizophrenia, drug-naïve, effectiveness

## Introduction

The early stages after a first episode of psychosis (FEP) represent a window of opportunity during which the effectiveness of clinical interventions can positively influence long-term outcomes (Robinson et al., 2005; Crespo-Facorro et al., 2016). The longer the duration of untreated psychosis (Harrigan et al., 2003) and active psychotic symptoms after initiating treatment (Pardo-de-santayana et al., 2020), the worse the clinical and functional outcomes in FEP patients. Consecutive relapses after a FEP are associated with longer time to remission (Emsley et al., 2013) and larger functional disability (Hui et al., 2018). Consequently, rapid symptomatic remission and relapse prevention represent critical aims in FEP treatment.

Although second-generation antipsychotic (SGA) prescription is the cornerstone of treatment in developed countries, comparisons between different SGAs remain scarce. In line with recent research, SGAs did not show substantial disparity between them concerning efficacy (Zhu et al., 2017a; Kim et al., 2021) or all-cause treatment discontinuation in FEP patients (McEvoy et al., 2007; Kahn et al., 2008; Gómez-Revuelta et al., 2021). However, attending to side effect profile and tolerability, differences appeared depending on the SGAs (Leucht et al., 2013; Huhn et al., 2019; Kim et al., 2021). Therefore, identifying the slight differences between SGA effectiveness might be a key point to personalize the most appropriate antipsychotic treatment that better suits each patient.

This study aims to provide information to guide the choice of FEP antipsychotic treatment, comparing 2 of the most widely used SGAs. To our knowledge, this is the second study comparing aripiprazole vs risperidone at a short-term phase (3 months) in patients suffering from an FEP (Robinson et al., 2015). Our research provides the largest patient sample analyzed to date comparing these drugs head-to-head in real-world conditions. Previous results from the aforementioned trial and other from our group (Gómez-Revuelta et al., 2021) demonstrated nonstatistically significant differences between aripiprazole and risperidone for

the treatment of FEP patients. Thus, the first aim of this clinical trial was to elucidate whether aripiprazole or risperidone may have a distinct effectiveness profile in this population. The main outcomes of effectiveness were the all-cause treatment discontinuation rate and the mean time to all-cause medication discontinuation. Secondly, according to previous meta-analyses (Huhn et al., 2019; Kim et al., 2021), our secondary aim was to address possible differences in efficacy and side effect profiles between these drugs, which may help in choosing the most suitable treatment in the short-term phase of treatment after a FEP.

## Experimental Procedures

### Study Settings

Data for the present investigation were obtained from the 12-week short-term phase of an ongoing 3-year longitudinal intervention program of FEP called PAFIP (Programa de Atención a las Fases Iniciales de Psicosis) conducted at the outpatient clinic and the inpatient unit of the University Hospital Marqués de Valdecilla, Spain (Son et al., 2021). Conforming to international standards for research ethics, this program was approved by the local institutional review board (CEIm of Cantabria/ROAC2014; EUDRACT: 2013-005399-16). Patients meeting inclusion criteria and their families provided written informed consent prior to their inclusion to the program.

### Participants

From February 2014 to October 2018, all referrals to PAFIP were screened for patients who met the following criteria: (1) 15–60 years old; (2) living in the catchment area; (3) experiencing their FEP; (4) no prior treatment with antipsychotic medication (antipsychotic naïve) or, if previously treated, and, in line with previous FEP research (Robinson et al., 2015), a total lifetime of

adequate antipsychotic treatment <6 weeks; and (5) DSM-IV criteria for brief psychotic disorder, schizophreniform disorder, schizophrenia, psychotic disorder not otherwise specified (NOS), 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 intellectual disability; (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 from the baseline visit.

## Study Design

This is a prospective, randomized, flexible-dose, open-label clinical trial comparing head-to-head aripiprazole and risperidone for the treatment of FEP patients. We used a simple randomization procedure to assign patients to each treatment group. Randomization consists of randomly assigning participants in a trial to 2 or more treatment or control groups. Randomization is one of the ways to avoid selection biases; its purpose is to enable comparisons in treatment allocation groups. Randomization based on a single sequence of random assignments is known as simple randomization. An automated computer-generated randomization list was drawn up. At baseline, out of 266 of individuals, 37 (13.9%) reported some prior antipsychotic treatment. The mean (SD) self-reported duration of prior treatment was 1.5 (1.3) weeks (range, 0.4–5.0 weeks). Before starting on the assigned drug, those participants ( $n=4$ ; 1.5%) under current antipsychotic treatment underwent a 2- to 4-day washout period. Antipsychotic doses expressed as chlorpromazine equivalents (CPZeq; mg/d) (Gardner et al., 2010) were as follows: risperidone 3–6 mg/d (300–600 CPZeq) and aripiprazole 5–30 mg/d (100–600 CPZeq). A rapid titration schedule (5 days), until minimum effective dose was reached, was used as a rule unless severe side effects occurred. All our patients reached the minimum effective dose of the interval prior to 5 days after starting antipsychotic treatment ( $n=252$ ; 94.7%, reached minimum effective dose on the first 72 hours after treatment start), but 2 patients experienced intolerable adverse events and discontinued treatment, failing to reach those doses. 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 medication, lormetazepam, 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 Undersøgelser (UKU) (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, 3 weeks, 6 weeks, and 12 weeks. All patients included in the analysis had completed at least the baseline and the 12-week assessments. Otherwise, they were considered as drop-out cases. The same trained psychiatrist (B.C.-F.) completed all clinical assessments.

## Outcome Measures

**Primary Outcome Measures: Effectiveness**—The main outcome of effectiveness was the all-cause treatment discontinuation rate, which is the percentage of all-cause discontinuation of the initially assigned treatment (patients who completed the 12-week follow-up assessment, and their initial antipsychotic treatment was switched during follow-up) and the mean time to all-cause medication discontinuation. Four reasons for the discontinuation were recorded: (1) non or insufficient efficacy, (2) significant side effects, (3) non-adherence, and (4) other causes. Insufficient efficacy was established at the treating physician's judgment only after at least 3 weeks of adequate treatment. Adherence to antipsychotic drugs was assessed by the information obtained from patients, close relatives, and staff (nurse, social worker, and psychiatrists) involved in the follow-up. According to previous definition (Gómez-Revuelta et al., 2018), 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 1 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 weekly during the first 4 weeks, at 6 weeks, and at 12 weeks.

**Secondary Outcome Measures: Efficacy and Safety**—The efficacy outcomes were the mean change from baseline to 12 weeks in BPRS, SAPS, and SANS total scores. Additional analyses included changes from baseline to 12 weeks in CGI, YMRS, and CDSS total scores. Patients were defined as responders to the optimum dose of antipsychotic if they had a  $\geq 30\%$  reduction of BPRS total score and a CGI severity score  $\leq 4$  after 12 weeks since the beginning of the treatment. To assure comparability along the different phases of the PAFIP program, these cut-off measures for response are in line with previous research from our group (Gómez-Revuelta et al., 2020) and other groups (Leucht, 2014). Side effects were evaluated using the UKU side effects rating scale. Only 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. Clinical assessments of side effects were completed at baseline, 6 weeks, and 12 weeks.

## Statistical Analyses

Our sample size calculation was based on results from previous studies. These studies were comparable with the current study in terms of length of follow-up, intervention used, and proposed primary outcome. The plan was to randomize 250 patients (including 20% inflation for dropouts) on risperidone and aripiprazole (1:1). Completion rates at 3-month follow-up of  $>90\%$  in previous clinical trials from our group have been reported, so we estimated there would be 200 study completers (i.e., 100 completers in each treatment group) at 3 months. Response was defined as a  $\geq 30\%$  improvement on the BPRS. To detect a response of  $\geq 30\%$  in BPRS total score, with 80% power, an alpha of 0.05 and SD of 10, we required 92 participants per group (2-sided) (Son et al., 2021).

All data were tested for normality (using Shapiro-Wilk test) and equality of variances (using Levene test). To ensure group comparability, baseline sociodemographic and clinical characteristics were tested by 1-way ANOVA or Kruskal-Wallis tests

for continuous variables or by chi-squared tests for qualitative variables.

Kaplan-Meier survival curves and log-rank tests 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 study period or by loss to follow-up.

For efficacy and safety measures, we performed both intention-to-treat analyses and per-protocol analysis. Differences between groups in the degree of change in clinical scores from baseline were evaluated with ANCOVA after baseline scores were controlled. Baseline values were used as covariate. Finally, comparisons of the discontinuation rates and the prevalence of side effects as well as the use of concomitant treatment between the 2 antipsychotics were carried out, performing chi-squared tests. R 3.6.1 was used for statistical analysis. Statistical tests were 2-tailed with a 95% confidence interval.

## Results

Of 299 drug-naïve individuals who were initially randomized to treatments, 33 were finally removed from the dataset after verifying they did not fully meet inclusion criteria or removed proper written consent during the first week. Thus, the final sample consisted of 266 participants who were randomly assigned to 2 different antipsychotic treatments: 130 patients were randomly assigned to the risperidone group, while 136 patients were assigned to the aripiprazole group (see Figure 1). After 12 weeks, 17 patients (6.39%) dropped out the study and 16 were censored for the survival analysis (10, aripiprazole and 6, risperidone). The retention rate was 94% (249/266). Of the 266 participants, 121 (45.5%) were female, and the mean age at inclusion was 32.3 years (SD=10.4). The most frequent diagnosis was schizophrenia (n=106, 39.8%), followed by schizophreniform disorder (n=81, 30.5%). No statistically significant differences were found between treatment groups in any of the baseline demographic and clinical characteristics (see Table 1).

### Primary Outcome Measures

**Effectiveness**—A total of 91 patients (34.21%) discontinued treatment by the end of 12-week follow-up. Despite a slightly higher all-cause discontinuation rate in the aripiprazole group (N=49; 36%) compared with the risperidone group (n=42; 32.3%), no statistically significant differences were observed between treatment groups regarding all-cause discontinuation ( $\chi^2=0.409$ ;  $P=.522$ ). Furthermore, survival curves did not show statistically significant differences regarding time to all-cause medication discontinuation (log rank=0.492;  $P=.48$ ) (see Figure 2). Non-efficacy was the main reason for discontinuation during the 12-week follow-up (n=36; 13.5%). Statistically significant differences concerning non- or insufficient efficacy were found ( $\chi^2=4.023$ ;  $P=.045$ ), showing a higher rate of discontinuation in the aripiprazole group (n=24, 17.6%) than in the risperidone group (n=12, 9.2%). Mean (SD) doses prior to discontinuation due to non- or insufficient efficacy were aripiprazole, 14.1 mg (SD=8.8) and risperidone, 3 mg (SD=1.7). Adjusted doses in CPZeq were 278.8 mg aripiprazole (SD=175.1) and 300 mg risperidone (SD=170.6). We did not find statistically significant differences on the remaining reasons considered for discontinuation (see Table 2). The mean time until all-cause discontinuation was 37.2 days (SD=18.3) for aripiprazole and 41.9 days (SD=24.5) for risperidone. There was no significant difference

between treatment groups in mean time to all-cause discontinuation (log rank  $\chi^2=-1.009$ ;  $P=.316$ ).

### Secondary Outcome Measures

**Efficacy**—The rates of clinical response were high and similar between treatment groups after performing intention-to-treat analyses ( $\chi^2=3.391$ ;  $P=.066$ ). Aripiprazole took some advantage ahead of risperidone and reached a higher rate of responders (aripiprazole, 92.3%; risperidone, 84.6%). Intention-to-treat analyses resulted in statistically significant differences in time to response (W=8183.5;  $P=.008$ ) and antipsychotic doses adjusted in chlorpromazine equivalents in patients who reached clinical response ( $\chi^2=2.160$ ;  $P=.032$ ). The mean time to response in the risperidone group was 25.7 days (SD=14.7), whereas patients in the aripiprazole arm needed 30.1 days (SD=18.9) to fulfil response criteria. In those patients who reached clinical response, mean antipsychotic doses at 12 weeks, adjusted in chlorpromazine equivalents, were 350.5 mg/d aripiprazole (SD=155.4) and 304 mg/d risperidone (SD=151.1). No statistically significant differences were found in any of the clinical categories measured at baseline at either 12 weeks or regarding changes between baseline and 12-week total scores (see Table 3). No additional differences in clinical response were recorded between treatment groups after performing per-protocol analysis; however, statistically significant differences in time to response were also replicated ( $P=.004$ ). The mean time to response in the risperidone group was 23.1 days (SD=11) and 26.2 days (SD=12.7) in the aripiprazole group after per-protocol analysis.

**Safety: Side Effects**—Intention-to-treat analysis showed increased fatigability (20.68% of the total sample) and weight gain (19.92% of the total sample) as the most frequent emergent side effects (see Table 4). However, no statistically significant differences between treatment groups were found. We did not find differences regarding body weight or body mass index increase between both treatments during the 12-week follow-up ( $t=-0.811$ ;  $P=.418$ ). Mean weight gain reached 4.7 kg (SD=5.6) in the aripiprazole group and 5.1 kg (SD=5.4) in the risperidone group ( $t=-0.461$ ;  $P=.645$ ). After per-protocol analysis, differences were equally nonstatistically significant. Rigidity was significantly more likely to affect the risperidone group compared with the aripiprazole group ( $F=6.206$ ;  $P=.014$ ). However, increased salivation affected more frequently the aripiprazole patients, and differences with the risperidone patients were statistically significant ( $\chi^2=3.924$ ;  $P=.048$ ). Concerning sexual side effects, all of them were significantly higher in the risperidone group: amenorrhoea ( $F=6.506$ ;  $P=.014$ ), decreased sexual desire ( $\chi^2=4.048$ ;  $P=.044$ ), erectile dysfunction ( $\chi^2=7.603$ ;  $P=.006$ ), and ejaculatory dysfunction ( $F=9.235$ ;  $P=.003$ ) (see Table 4).

**Extrapyramidal Symptoms**—No significant differences in the percentage of patients with treatment-emergent-parkinsonism (a total score >3 on the SARS at 12-week assessment, given a total score ≤3 at baseline) or treatment-emergent akathisia (BAS global score ≥2 at 12-week assessment, given a global score <2 at baseline) were registered between treatment groups after intention to treat. Neither did we find significant differences in the UKU akathisia item or on the akinesia item between both treatments at 12-week assessment. We found no statistically significant differences between treatment groups after performing per-protocol analysis.

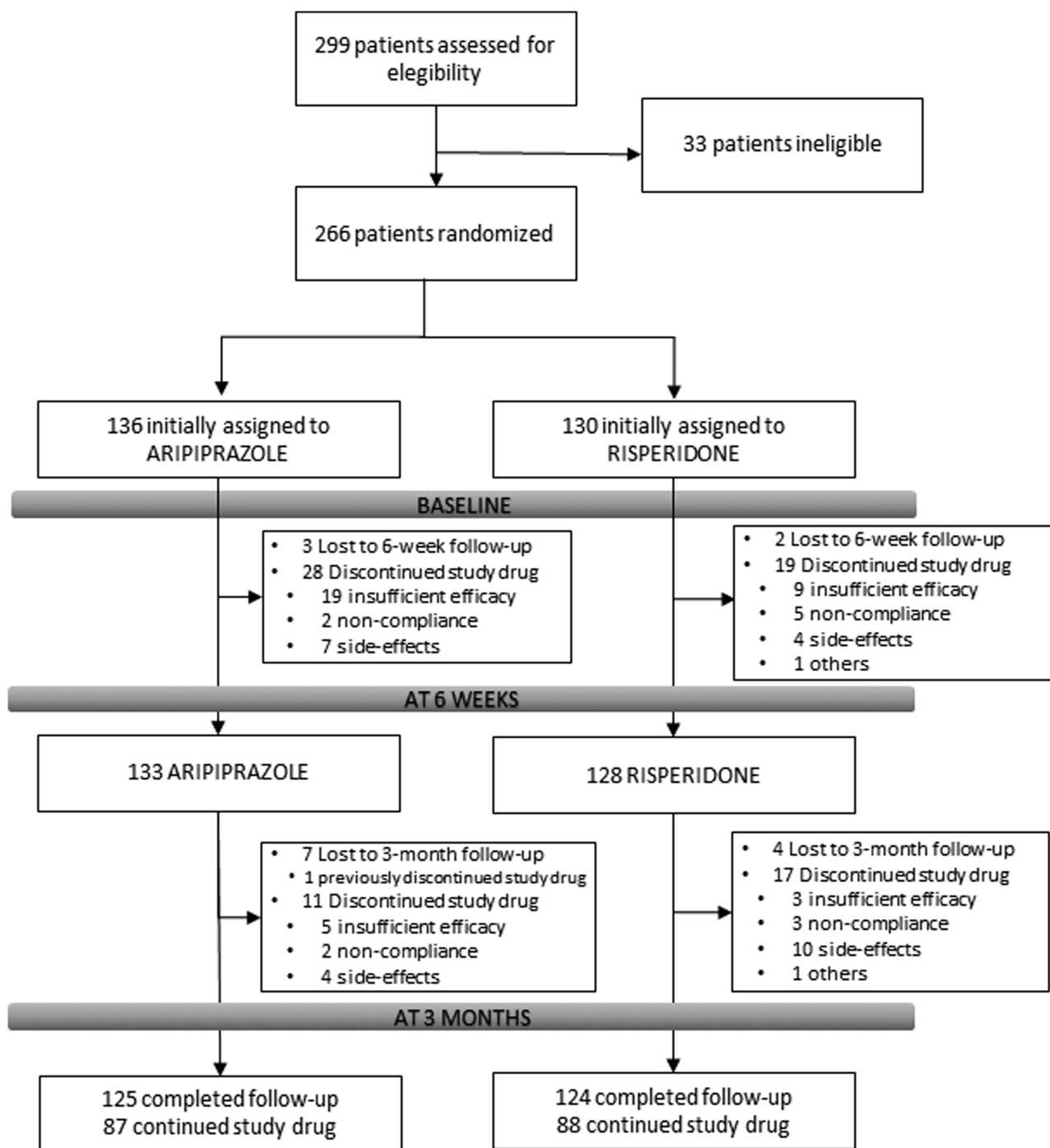


Figure 1. Flow diagram of participant through the phases of the randomized trial.

**Concomitant Medication Use**—Intention-to-treat analysis of 12-week data did not show differences regarding the usage of hypnotics, benzodiazepines, antidepressants, mood stabilizers, and anticholinergics between treatment arms. Similarly, during the 12-week follow-up, there were no statistically significant differences in the usage of any of these treatments. Benzodiazepines were the most frequent concomitant medication ( $n=191$ ; 76.7%) used during this period. However, at the 12-week endpoint, anticholinergics were the most common concomitant medication employed ( $n=72$ ; 30.3%) (see Table 5).

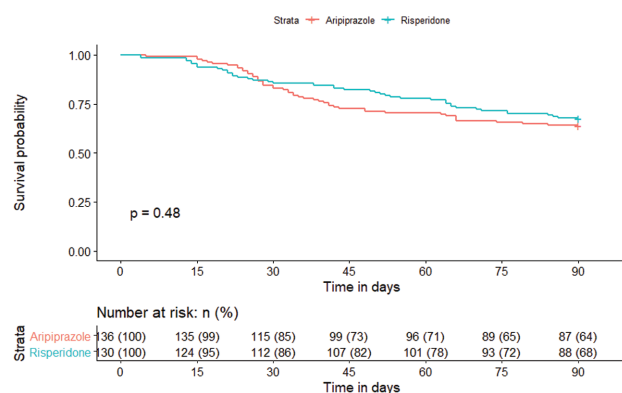
No statistically significant differences were registered after performing per protocol analyses.

## Discussion

To our knowledge, this is the second clinical trial comparing the effectiveness of aripiprazole and risperidone head-to-head for the short-term treatment of patients suffering a FEP. In this clinical trial, we studied 266 patients and found a high retention rate at 12-week follow-up (94% of completers), which is prominently

**Table 1.** Demographic and Clinical Characteristics of 266 Drug-Naïve Patients With a First Episode of Non-affective Psychosis

	Aripiprazole		Risperidone		Total	
	n = 136		n = 130		n = 266	
	Mean	SD	Mean	SD	Mean	SD
Age at inclusion	32.0	10.7	32.6	10.1	32.3	10.4
Age at psychosis onset	31.3	10.7	31.5	10.2	31.4	10.4
Duration Untreated Illness (DUI), mo	14.0	24.9	17.7	40.3	15.8	33.3
Duration Untreated Psychosis (DUP), mo	10.6	23.4	14.3	38.7	12.4	31.9
Education, y	9.9	3.2	10.0	3.2	10.0	3.2
	n	%	n	%	n	%
Diagnosis (schizophrenia)	57	41.9	49	37.7	106	39.8
Diagnosis						
Schizophrenia	57	41.9	49	37.7	106	39.8
Brief psychotic disorder	21	15.4	23	17.7	44	16.5
Psychotic disorder not otherwise specified	12	8.8	17	13.1	29	10.9
Schizophreniform disorder	44	32.4	37	28.5	81	30.5
Schizoaffective disorder	2	1.5	1	0.8	3	1.1
Delusional disorder	0	0.0	3	2.3	3	1.1
Gender (male)	74	54.4	71	54.6	145	54.5
Ethnicity (White)	115	84.6	113	86.9	228	85.7
Family psychiatric history (yes)	39	28.7	38	29.5	77	29.1
Hospitalization at inclusion (yes)	104	76.5	103	79.2	207	77.8
Educational level (elementary)	68	51.1	58	46.0	126	48.6
Student—baseline (yes)	36	26.9	24	19.0	60	23.1
Socioeconomic status of parents (Not/low qualified workers)	68	52.3	79	63.7	147	57.9
Urban area—baseline (urban area)	97	71.3	88	67.7	185	69.5
Living with parents—baseline (yes)	71	53.8	57	45.2	128	49.6
Single—baseline (yes)	99	73.9	81	64.3	180	69.2
Unemployed—baseline (yes)	57	43.2	47	37.6	104	40.5
Tobacco—baseline (yes)	62	47.3	61	49.2	123	48.2
Cannabis—baseline (yes)	59	43.4	48	37.2	107	40.4
Amphetamines—baseline (yes)	5	3.7	7	5.6	12	4.6
Cocaine—baseline (yes)	14	10.3	15	11.7	29	11.0
Alcohol—baseline (yes)	50	37.3	46	36.8	96	37.1

**Figure 2.** Kaplan-Meier survival graph: any cause discontinuation.

higher than retention rates found in other clinical trials comparing short-term effectiveness of aripiprazole and risperidone in patients suffering an FEP (Robinson et al., 2015).

### Primary Outcome Measures

**Effectiveness**—In line with previous studies comparing aripiprazole and risperidone in first-episode schizophrenia

spectrum patients (Robinson et al., 2015; Gómez-Revuelta et al., 2021), no significant differences regarding all-cause discontinuation rates of the initially prescribed medication were detected between treatment groups. The global all-cause discontinuation rate in our study (34.2%) is comparable with that of similar short- and medium-term clinical trials weighing the effectiveness between different SGAs (Johnsen et al., 2010; Crespo-Facorro et al., 2013; Gómez-Revuelta et al., 2018).

Similar research (Crespo-Facorro et al., 2013; Gómez-Revuelta et al., 2018), suggested that non- or insufficient efficacy was, globally, the main reason for discontinuation during the short-term follow-up after an FEP. In the aripiprazole group, lack of efficacy represented the main reason for discontinuation because it involved almost one-half of the patients who abandoned their first-assigned antipsychotic treatment (24/49=48.9%). This was not the case for the risperidone group, in which discontinuation due to lack of efficacy accounted for only less than one-third of the total patients who discontinued treatment (12/42=28.5%), and adverse events were the main reason for discontinuation (14/42=33.3%). These data are consistent with a recent meta-analysis comparing aripiprazole vs D2 antagonists (Kim et al., 2021), where aripiprazole showed significantly greater discontinuation rates due to insufficient efficacy than risperidone in short-term trials. In our study, after adjustment

**Table 2.** Treatment Doses Before Discontinuation and Any-cause Discontinuation Rates by Allocated Causes

	Aripiprazole		Risperidone		Total		Statistic	Value	P
	n=136		n=130		n=266				
	Mean	SD	Mean	SD	Mean	SD			
Dose before discontinuation	13.3	9.3	3.1	1.5	8.6	8.6			
Dose before discontinuation (CPZ Eq)	267.0	183.8	310.7	152.0	287.4	170.2	t	-1.218	.227
	n	%	n	%	n	%			
Discontinuation for any cause (yes)	49	36.0	42	32.3	91	34.2	$\chi^2$	0.409	.522
Discontinuation because of insufficient efficacy (yes)	24	17.6	12	9.2	36	13.5	$\chi^2$	4.023	.045
Discontinuation because of noncompliance (yes)	3	2.2	8	6.2	11	4.1	$\chi^2$	2.613	.106
Discontinuation because of adverse effect (yes)	11	8.1	14	10.8	25	9.4	$\chi^2$	0.561	.454
Discontinuation because other causes (yes)	1	0.7	2	1.5	3	1.1	Fisher	0.385	.615
Discontinuation because of dropout (yes)	10	7.4	6	4.6	16	5.3	$\chi^2$	0.881	.348

Abbreviations: CPZ Eq: chlorpromazine equivalents

**Table 3.** Intention-to-Treat Sample: Psychopathological Characteristics at Baseline and 12 Weeks and Clinical Changes During the Follow-Up

	Aripiprazole		Risperidone		Total		Statistic	Value	P
	n=125		n=124		n=249				
	Mean	SD	Mean	SD	Mean	SD			
CGI									
Baseline	6.4	0.9	6.4	0.9	6.4	0.9	W	6740.000	.547
12 wk	2.2	1.4	2.4	1.6	2.3	1.5	W	6874.500	.771
12-wk change from baseline	-4.2	1.6	-4.1	1.8	-4.1	1.7	t	-0.420	.675
12-wk change from baseline (covariated)	-4.2	0.1	-4.0	0.1			F	0.423	.516
BPRS total									
Baseline	68.0	18.1	71.2	17.2	69.6	17.7	t	-1.404	.162
12 wk	31.1	9.8	32.9	10.1	32.0	10.0	W	6231.500	.160
12-wk change from baseline	-36.9	17.8	-38.3	17.9	-37.6	17.8	t	0.606	.545
12-wk change from baseline (covariated)	-38.3	0.9	-36.9	0.9			F	1.129	.289
SAPS									
Baseline	15.3	4.8	15.4	5.1	15.3	5.0	t	-0.296	.767
12 wk	1.1	2.7	1.0	2.4	1.0	2.6	W	6980.000	.801
12-wk change from baseline	-14.2	5.1	-14.4	5.5	-14.3	5.3	t	0.325	.745
12-wk change from baseline (covariated)	-14.3	0.2	-14.3	0.2			F	0.018	.892
SANS									
Baseline	5.5	6.0	5.0	6.0	5.2	6.0	W	7117.500	.514
12 wk	4.3	5.1	5.1	5.8	4.7	5.5	W	6387.500	.431
12-wk change from baseline	-1.2	6.5	0.1	6.3	-0.6	6.4	t	-1.495	.136
12-wk change from baseline (covariated)	-1.0	0.5	-0.1	0.5			F	1.905	.169
CDSS									
Baseline	1.7	2.5	1.7	2.8	1.7	2.6	W	7168.500	.955
12 wk	1.4	3.0	2.0	3.5	1.7	3.3	W	6418.000	.129
12-wk change from baseline	-0.3	3.8	0.3	4.5	0.0	4.2	W	6443.000	.181
12-wk change from baseline (covariated)	-0.3	0.3	0.3	0.3			F	1.862	.174
YMRS									
Baseline	13.7	6.5	13.1	6.0	13.4	6.2	t	0.658	.511
12 wk	1.3	2.5	1.4	3.0	1.3	2.7	W	7553.000	.295
12-wk change from baseline	-12.3	6.9	-11.8	6.4	-12.0	6.6	t	-0.633	.527
12-wk change from baseline (covariated)	-12.1	0.2	-12.0	0.3			F	0.006	.937

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. 12-week change from baseline (covariated): 12-week change from baseline after controlling for baseline.

by chlorpromazine equivalents we found the usage of lower doses of aripiprazole compared with risperidone at this point. Regarding that, 2 recent meta-analysis assessing antipsychotic dose-response in acute schizophrenia (Leucht et al., 2020; Sabe et al., 2021) suggested that the mean dose that produces 95%

of the maximum reduction of patients' symptoms was approximately 11–12 mg/d for aripiprazole and 6.3–7.7 mg/d for risperidone. According to this information, we can assume that differences concerning non- or insufficient efficacy in the aripiprazole group may not be caused by insufficient dosing.

**Table 4.** Intention-to-treat sample: Moderate or severe treatment-emergent side effects that occurred at a rate of at least 5% in either treatment group.

	Aripiprazole		Risperidone		Total		Statistic	Value	p
	N=125		N=124		N=249				
	N	%	N	%	N	%			
<b>Psychic</b>									
Concentration Difficulties - 12-weeks	6	5.0	1	0.8	7	2.9	Fisher	3.636	0.120
Increased Fatigability - 12-weeks	27	22.5	28	23.5	55	23.0	$\chi^2$	0.036	0.850
Sleepiness - 12-weeks	17	14.2	16	13.4	33	13.8	$\chi^2$	0.026	0.872
Increased Duration of Sleep - 12-weeks	17	14.2	14	11.8	31	13.0	$\chi^2$	0.305	0.581
<b>Neurologic</b>									
Rigidity - 12-weeks	0	0.0	6	5.0	6	2.5	Fisher	6.206	0.014
Akinesia - 12-weeks	14	11.7	17	14.3	31	13.0	$\chi^2$	0.363	0.547
Akathisia - 12-weeks	12	10.0	8	6.7	20	8.4	$\chi^2$	0.837	0.360
<b>Autonomic</b>									
Increased Salivation - 12-weeks	10	8.3	3	2.5	13	5.4	$\chi^2$	3.924	0.048
<b>Other</b>									
Weight gain - 12-weeks	28	23.3	25	21.0	53	22.2	$\chi^2$	0.187	0.665
Amenorrhoea - 12-weeks	1	1.8	8	15.1	9	8.2	Fisher	6.506	0.014
Diminished Sexual Desire - 12-weeks	3	2.5	10	8.4	13	5.4	$\chi^2$	4.048	0.044
Erectile Dysfunction - 12-weeks	1	1.6	10	15.2	11	8.5	$\chi^2$	7.603	0.006
Ejaculatory Dysfunction - 12-weeks	0	0.0	9	13.6	9	7.0	Fisher	9.235	0.003

**Table 5.** Concomitant treatments used at 12-weeks or any time during the 12-weeks follow-up.

	Aripiprazole		Risperidone		Total		Statistic	Value	p
	N=125		N=124		N=249				
	N	%	N	%	N	%			
<b>At the end of 12-weeks follow-up</b>									
Hypnotics	26	22.0	29	24.2	55	23.1	$\chi^2$	0.152	0.696
Benzodiazepines	25	21.2	38	31.7	63	26.5	$\chi^2$	3.357	0.067
Antidepressants	18	15.3	25	20.8	43	18.1	$\chi^2$	1.251	0.263
Mood stabilizers	5	4.2	4	3.3	9	3.8	Fisher	0.134	0.748
Anticholinergics	41	34.7	31	25.8	72	30.3	$\chi^2$	2.240	0.135
<b>Any time during 12-weeks follow-up</b>									
Hypnotics	89	71.2	88	71.0	177	71.1	$\chi^2$	0.002	0.968
Benzodiazepines	96	76.8	95	76.6	191	76.7	$\chi^2$	0.001	0.972
Antidepressants	20	16.0	29	23.4	49	19.7	$\chi^2$	2.149	0.143
Mood stabilizers	7	5.6	5	4.0	12	4.8	$\chi^2$	0.334	0.564
Anticholinergics	52	41.6	39	31.5	91	36.5	$\chi^2$	2.765	0.096

Interestingly, our experience differed in attending to antipsychotic dose-response as lower doses of risperidone may be highly efficacious.

Significant side effects were the second reason for discontinuation in both groups, with 9.4% of the total sample showing discontinuation treatment due to this cause. These results are consistent with a recent meta-analysis (Kim et al., 2021) where no statistically significant differences between groups were found regarding discontinuation due to side effects. It is of note that non-adherence was a rare cause for discontinuation as only 4.1% of the total sample abandoned initial treatment due to this reason.

Regarding mean time until all-cause discontinuation, though not statistically significant, it was longer in the risperidone group (41.9 days, SD = 24.5) compared with the aripiprazole group (37.2 days, SD = 18.3). As we mentioned above, non- or insufficient efficacy was the most frequent reason for all-cause treatment discontinuation. In this sense, during the last decades, still inconclusive controversy has surrounded the optimum timing

for the antipsychotic switch in case of non-efficacy after FEP. The notion of a late onset of antipsychotic drug action influenced clinical decisions and led clinical guidelines to recommend a treatment regimen of 4–6 weeks before switching treatment due to non-efficacy (Johnstone et al., 1978). However, this paradigm was questioned after the emergence of data suggesting an earlier onset for antipsychotic treatment action (Leucht et al., 2005; Agid et al., 2006). Some research proposed that its effects may be appreciated within the first 24 hours after initiating treatment (Kapur et al., 2005), with the greater clinical improvement along the first 2 weeks. In a meta-analysis carried out in chronic patients with schizophrenia (Samara et al., 2015), it was pointed out that non-improvement within the first 2 weeks would be a clinical predictor of a subsequent lack of response. This finding suggests an early treatment switch in these patients, preventing unnecessary long-term exposure, which may unlikely be clinically beneficial. However, the same meta-analysis (Samara et al., 2015) also pointed out that FEP patients seem to present



different response patterns compared with chronic patients, as shown in different studies (Derks et al., 2010; Gallego et al., 2011) indicating a later onset of response in FEP. It is remarkable that in our clinical trial, non-efficacy criteria were applied only to those patients who had received optimal doses for at least 3 weeks. Importantly, a rapid titration schedule was followed, when possible, in most of cases in our clinical practice in balance with safety and tolerability issues. Thus, attending to these factors, titration could not be that fast in some patients.

## Secondary Outcome Measures

**Efficacy**—A high clinical response rate was reached at 12-week follow-up, with aripiprazole (92.3%) showing some advantage compared with risperidone (84.4%). Response rates were higher in our study than other previous studies comparing head-to-head aripiprazole and risperidone (Robinson et al., 2015; Gómez-Revuelta et al., 2021). This finding may be explained by the fact that we studied people suffering their FEP, and most of them were antipsychotic naïve (86.5% in this study vs 70% in previous research) (Robinson et al., 2015). According to previous studies, patients experiencing their FEP present higher response rates to antipsychotic treatment than chronic patients (Gaebel et al., 2002; Ohlsen et al., 2004). Furthermore, in line with other studies, antipsychotic naivety is another determinant predictor for better antipsychotic response in patients suffering an FEP (Zhu et al., 2017b). In addition, other possible reasons to explain these differences are the higher duration of untreated psychosis (DUP) periods and higher schizophrenia diagnosis rates registered in other research (Robinson et al., 2015). The cumulative effect of these circumstances may represent the difference for the higher rates of response on our sample.

In our study, we did not find differences between aripiprazole or risperidone performance regarding positive, negative, or affective symptoms (BPRS, SANS, SAPS, CGI, CDSS, YMRS). These results contrast with data from some meta-analysis assessing antipsychotic efficacy in which risperidone was more efficacious than aripiprazole after measurement of total PANSS and/or BPRS scores (Leucht et al., 2013; Huhn et al., 2019). In addition, no differences were observed in our study according to negative symptoms, a dimension that was associated with some advantages for patients under aripiprazole treatment in previous studies (Robinson et al., 2015; Huhn et al., 2019). However, it is important to point out that such differences were modest and limited to the avolition-apathy domain in 1 of these studies (Robinson et al., 2015) and that the other studies (Huhn et al., 2019) were focused on multi-episode schizophrenia patients. It is important to point out that aripiprazole performed significantly better than haloperidol regarding negative symptoms, which may be explained by a larger trend in the emergency of secondary negative symptoms related to haloperidol treatment. According to our results, a recent meta-analysis comparing the efficacy and tolerability of aripiprazole vs different D2-receptor antagonists in the early course of schizophrenia (including risperidone) found no advantages for aripiprazole regarding negative symptoms (Kim et al., 2021).

**Safety**—In our study, discontinuation because of side effects was low ( $n=25$ ; 9.4%), and we found several differences between treatments concerning side effects. The impact of sexual side effects on treatment discontinuation is well known, especially in men (Montejo et al., 2010). In line with previous studies of our group (Gómez-Revuelta et al., 2020) and others (McEvoy et al., 2007; Huhn et al., 2019), all sexual side effects were significantly more frequent in the risperidone arm. Rigidity was also

significantly more frequent in the risperidone group, which is consistent with other studies showing a higher rate than other SGAs (Leucht et al., 2013).

Concerning weight gain or body mass index increase at 12-week follow-up, there were no differences between groups. Previous studies comparing aripiprazole and risperidone in FEP patients (Robinson et al., 2015) reported similar data. Moreover, a meta-analysis focused on the study of antipsychotic-induced weight gain in FEP patients showed weight gain related to aripiprazole and risperidone use at short term ( $\leq 12$  weeks) (Tek et al., 2016). This analysis also pointed to the association between weight gain and duration of antipsychotic use. This result is in line with some of our results: interestingly, at our 6-week report of this clinical trial (Gómez-Revuelta et al., 2021), we found that <10% of the participants suffered from weight gain compared with 22.2% at our 12-week study. In addition, it is not only a question of how many people gain weight but a question of the magnitude of that gain, which is certainly relevant. We found that patients in both groups experienced a 2-point increase in their body mass index after only 3 months since treatment kick-off. These data may reflect a necessity for specific interventions on diet and physical activity beginning around this timeframe to prevent further metabolic issues.

According to certain studies, salivation is not a common adverse event with either aripiprazole or risperidone treatment (Leucht et al., 2013). Nonetheless, sialorrhea produces medical and psychosocial complications and usually can represent a socially stigmatizing side effect related with treatment discontinuation (Prahara et al., 2006). In our research, increased salivation resulted statistically more frequently with aripiprazole than with risperidone, though its global prevalence remained low ( $n=13$ ; 5.4%).

No statistical differences in akathisia between aripiprazole and risperidone were observed. This agrees with a previous study concerning acute akathisia after an FEP (Juncal-Ruiz et al., 2017). This analysis found that aripiprazole and risperidone had a higher incidence of acute akathisia than other SGAs but did not significantly differ. These results stand in contrast to data suggesting that aripiprazole was responsible for higher akathisia emergence than risperidone (Robinson et al., 2015). We can find strong evidence suggesting that aripiprazole (in short-term trials) was more frequently associated with akathisia compared with D2 antagonists, especially quetiapine and olanzapine (Kim et al., 2021). This is consistent with a recent network meta-analysis involving patients with FEP, where aripiprazole was less favorable than quetiapine and olanzapine for akathisia (Zhu et al., 2017a). Nevertheless, aripiprazole was not associated with higher discontinuation due to adverse events than D2 receptor antagonists, including quetiapine and olanzapine, indicating that the severity of akathisia may have been tolerable. Aripiprazole-induced akathisia may be attributed to its pro-serotonergic effects as well as its functional selectivity for D2 receptors. In the case of the latter, aripiprazole may be acting as a full antagonist in certain brain regions (e.g., striatum) where there are higher levels of D2 receptor expression (Kim et al., 2021).

In relation to concomitant medication used at the end of the 12-week period, there were no statistically significant differences. Most patients required some concomitant treatment during the 12-week follow-up period, with hypnotics and benzodiazepines leading the most widely used concomitant medications in both treatment groups with no statistically significant differences between aripiprazole and risperidone arms for the usage of each of those drugs. Nonetheless, at the end of the

follow-up period the use of these treatments has dramatically fallen globally and in each treatment arm, with less than one-quarter of patients requiring treatment with benzodiazepines and/or hypnotics. Actually, after 12-week follow-up, anticholinergics become the leading concomitant treatment used globally in both treatment arms. In line with results from a recent meta-analysis (Kim et al., 2021), anticholinergic agents were more frequently used in the aripiprazole group. There is no clear explanation for a greater use of anticholinergic agents in the aripiprazole arm because there were no differences in BAS and SAS scores between groups. On the other hand, benzodiazepines were more frequently used in the risperidone group.

### Limitations and Strengths

Our study has potential limitations that must be considered in the interpretation of the results. First, as a pragmatic 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 2 antipsychotics is limited. Second, the study was focused on comparing effectiveness of the 2 antipsychotics during the first 12-week treatment phase after an FEP diagnosis, which may have limited value for the long-term outcome of FEP patients. On the other hand, it is of the utmost importance to choose a first treatment that provides efficacy and tolerability and after which the patient feels acceptable, because these factors could increase the probabilities of adherence and could have an essential impact in modifying the long-term functional prognosis of these patients. Third, heterogeneity of the disorders included in the FEP group could represent a limiting factor for the predictive value of the treatments for the long-term outcome. Nevertheless, this heterogeneity of the diagnoses in our sample also represents the reality that most clinicians experiment in their real practice when treating FEP patients, and it is similar to previous studies of our group and other groups (Crespo-Facorro et al., 2013; Robinson et al., 2015). Fourth, treatment compliance measures were collected from self-reported and close observers (family members and social assistants) but not from antipsychotic blood levels. This fact could have an impact on the accuracy of discontinuation measures due to noncompliance. Optimal doses of antipsychotics within the 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.

On the other hand, to our knowledge, with including 266 patients, this is the largest antipsychotic naïve short-term phase FEP effectiveness study comparing head-to-head aripiprazole vs risperidone. It was performed in a well-characterized and homogeneous sample, and most patients (86.5%) were antipsychotic naïve prior to study intake.

### Conclusions

After an FEP, it is of the utmost importance to identify discontinuation patterns, risks, and benefits from different SGA treatments to personalize first antipsychotic treatment choice. In our study, we found no differences regarding effectiveness between risperidone and aripiprazole, with both being highly effective drugs for the treatment of FEP patients in the short-term phase. This research reflects small, albeit nonstatistically significant differences in terms of efficacy. However, concerning side effects, a determinant issue to prevent discontinuation at and

after the short-term phase, sexual side effects and rigidity were significantly more frequent in the risperidone group, whereas sialorrhea was more frequent in the aripiprazole group. Finally, weight gain was a major issue in both groups, and developing effective approaches towards its prevention and treatment may be a priority.

Despite the importance of efficacy during the acute phase treatment of an FEP, differences in side effect profiles and patient preferences are essential factors to determine acceptability and good adherence to antipsychotic treatment. Therefore, the process of optimizing long-term outcome by pursuing personalized interventions focused on each patient's specific characteristics, preferences, or needs should be initiated as soon as possible after FEP diagnosis.

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