Aripiprazole, Ziprasidone and Quetiapine in the treatment of first-episode nonaffective psychosis: A 12-week randomized, flexible-dose, open-label trial

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1. Introduction

Second generation (‘atypical’) antipsychotics (SGAs) are the first-line drug treatment for individuals suffering from first-episode schizophrenia (Lieberman, 1996). SGAs are not a homogeneous group and clinical effects and profiles of side-effects differ between SGAs (Tandon et al., 2008). An optimal clinical efficacy and a good tolerability are important factors for ensuring successful clinical effectiveness. Differences among antipsychotics in terms of effectiveness have turned out to be a topic for increasing research interest, although comparisons between the different second generation antipsychotics (SGAs) are scarce. We aimed to compare the clinical effectiveness in the short-term of Aripiprazole, Ziprasidone and Quetiapine in the treatment of first-episode schizophrenia-spectrum disorders.

In first-episode psychosis, SGAs have shown higher treatment effectiveness compared to first generation antipsychotics (FGAs) (findings primarily driven by haloperidol) (Green et al., 2006; Kahn et al., 2008; Crespo-Facorro et al., 2011, 2012). Both SGAs and low doses of first generation antipsychotics (FGAs) are similarly efficacious in improving active psychotic symptomatology in first-episode psychosis (Emsley, 1999; Sanger et al., 1999; Lieberman et al., 2003; Crespo-Facorro et al., 2006). 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). The meta-analysis by Leucht et al. (2009) established that a head-to-head comparison of SGAs in the treatment of schizophrenia revealed no differences between agents regarding effectiveness measures. Nonetheless, slight differences between SGAs in the improvement of positive symptoms have been described. In a recent study, Aripiprazole and Ziprasidone showed significantly higher effectiveness than Quetiapine in the acute (6 weeks) treatment of first-episode schizophrenia-spectrum disorders (Crespo-Facorro et al., 2013). Most of the medium-term...
randomized studies have shown similar rates of all-cause treatment discontinuation in first episode patients treated with different SGAs (McEvoy et al., 2007; Kahn et al., 2008; Crespo-Facorro et al., 2011). We undertook this study with the major objective of comparing the clinical effectiveness of three commonly used SGAs (Aripiprazole, Ziprasidone and Quetiapine) in the treatment of non-affective psychosis individuals and of which previous direct comparisons have not been reported.

We undertook this study with the major objective of comparing the clinical effectiveness in the short-term of Aripiprazole, Ziprasidone and Quetiapine in the treatment of first–episode non-affective psychosis individuals. Direct comparisons between these three commonly used antipsychotics have been not reported. We hypothesize that the likely disparity in efficacy and side-effect profiles may mediate differences in effectiveness between SGA treatments in real-world clinical practice.

2. Method

2.1. Study setting and financial support

Data for the present investigation were obtained from an ongoing epidemiological and three-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. The Mental Health Services of Cantabria provided funding for implementing the program. No pharmaceutical company supplied any financial support to this study.

2.2. 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; and 5) DSM-IV criteria for brief psychotic disorder, schizophreniaiform 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 (SCID-I) (First et al., 2001), carried out by an experienced psychiatrist 6 months after 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 had not received previous antipsychotic treatment, regardless of the duration of psychosis.

2.3. Study design

This is a prospective, randomized, flexible-dose, open-label study. At study intake, all patients but eight were antipsychotic-naïve. Dose ranges were 5–30 mg/day Aripiprazole, 40–160 mg/day Ziprasidone and 100–600 mg/day Quetiapine. Rapid titration schedule (5-day), until optimal dose was reached, was used as a rule unless severe side-effects occurred. 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. Anti-muscarinic medications, Lorazepam and Clonazepam were permitted for clinical reasons. No anti-muscarinic agents were administered prophylactically. Antidepressants (Sertraline) and mood stabilizers (lithium) were permitted if clinically needed.

2.4. Outcome measures

2.4.1. Primary outcome measures: effectiveness

The main outcomes of effectiveness were the percentage of discontinuation of the initially assigned treatment (patients who completed the 3 months follow-up assessment and changed initial antipsychotic) and the mean time to all-cause medication discontinuation (accepted indexes of medication effectiveness). Four reasons for 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 three weeks of treatment.

2.4.2. Secondary outcome measures: efficacy and safety

The efficacy outcomes were the mean change from baseline to 3 months in BPRS, SAPS and SANS total scores. Additional analyses included changes from baseline to 3 months in CGS, YMRS, and CDSS total scores. The patients were defined as responders to the optimum dose of antipsychotic at 6 weeks if there was a >40% reduction of the BPRS score 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 score 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 10% in either treatment group were 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 and 3 months.

2.5. Statistical analyses

To ensure group comparability, baseline sociodemographic and clinical characteristics were tested by 1-way analysis of variance (ANOVA) or χ² test for categorical variables. The proportion of patients who were compliant (good adherence), the frequency of patients who used hypnotics, mood stabilizers, anti-muscarinic 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. Differences between groups in the degree of change in clinical scores from baseline were evaluated with analysis of covariance after control for baseline scores was performed. All
patients included in the analysis had baseline and 3-month assessments. Within-group comparisons were also explored by using the t-test to analyze baseline to end-point differences. By using Fisher’s exact and chi-square tests, evaluated categorical data were assessed. All hypotheses were tested by using a two-sided significant level of 0.05.

The Statistical Package for Social Science (SPSS), 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.

3. Results

3.1. Description of study cohort

Fig. 1 shows the trial profile. Of the 224 individuals who were initially randomized to treatments, 22 were finally removed from the data set because it was verified that they did not fully meet the inclusion criteria or they did not give or removed written consent during the first week. Thus, 202 patients who gave written consent to their participation in the study and fulfilled the inclusion criteria at six months were included in our analyses. At baseline, only 8 (4.0%) of the 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 3 months was small (N = 28; 13.86%). Two persons committed suicide during 3-month follow up (1 Aripiprazole and 1 Quetiapine). All but 10 individuals were white Caucasian. Demographic and clinical characteristics of patients are shown in Table 1.

Mean (SD) and median antipsychotic doses at 3 months were: Aripiprazole = 16.8 (7.8) mg/day and 15.0 mg/day, Ziprasidone = 87.7 (30.0) mg/day and 80.0 mg/day, and Quetiapine = 358.3 (157.2) mg/day and 300.0 mg/day.

3.2. Primary outcome measures

3.2.1. Treatment discontinuation rate and time to discontinuation

The treatment discontinuation rate for any cause differed significantly between treatment groups ($\chi^2 = 21.334; p < 0.001$) (Table 2). Patients on Quetiapine showed a higher rate (61.3%) of treatment discontinuation than Aripiprazole (23.1%) and Ziprasidone (37.1%) individuals. Insufficient efficacy in the Quetiapine group was the main reason for discontinuation rate differences ($\chi^2 = 20.223; p < 0.001$). The mean

![Flow diagram of subject through the phases of the randomized trial.](image-url)
time (days) to all-cause discontinuation was 37.39 (95% CI, 27.71–47.07) for Aripiprazole, 38.26 (95% CI, 29.19–43.40) for Quetiapine and 35.92 (95% CI, 28.44–47.07) for Ziprasidone. There was a significant difference between groups in time to discontinuation (Log Rank = 3.3.1. Clinical efficacy
There were no statistically significant differences in the severity of symptoms at baseline and at 3 months between the treatment groups (Table 3). The univariate ANOVA analysis, after controlling by CDSS total score at baseline, also showed differences between treatments in reducing depressive symptoms (F = 4.404; p = 0.014). The post hoc pair-wise analysis revealed a lower effect of Ziprasidone compared to Aripiprazole and Quetiapine. The rate of responders (≥40% BPRS & ≤4 CGI) differed between groups (Aripiprazole 76.4%; Ziprasidone 55.8%; Quetiapine 64.6%; F = 5.950; p = 0.051). This difference in the rate of responders between groups was statistically significant when the criteria of at least a 50% decrease in total BPRS at baseline was used as a cutoff (Aripiprazole 61.1%; Ziprasidone 36.5%; Quetiapine 50.0%; F = 7.303; p = 0.026).

3.3.2. Safety

3.3.2.1. Extrapyramidal symptoms. Intention-to-treat analyses showed no significant differences in the increment of extrapyramidal signs at 3 months (SARS total score) between treatments (F = 1.513;
The percentage of patients with treatment-emergent parkinsonism (a total score higher than 3 on the SARS at 6-weeks or/and 3-month assessments, given a total score of 3 or less at baseline) was not statistically different between treatment arms (Aripiprazole = 13.9%; Ziprasidone = 15.4% and Quetiapine 4.0%; $\chi^2 = 3.940; p = 0.139$), although it could be of clinical relevance. Extrapyramidal signs were more severe and more frequent with Aripiprazole and Ziprasidone than with Quetiapine.

There was no significant difference between treatments in the severity of akathisia (BAS total score) at 3 months assessment ($F = 2.616; p = 0.076$). It is of note that a higher number of individuals in the Aripiprazole- and Ziprasidone-treated groups (25.0% in both groups) experienced treatment-emergent akathisia (BAS global score of 2 or more at 6-week or/and 3-month evaluations, given a global score of less that 2 at baseline visit) compared to Quetiapine-treated subjects ($\chi^2 = 6.408; p = 0.041$).

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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 3 months and clinical changes during the follow up period.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (N = 174)</th>
<th>Quetiapine (N = 50)</th>
<th>Ziprasidone (N = 52)</th>
<th>Aripiprazole (N = 72)</th>
<th>F(df = 2)</th>
<th>P</th>
</tr>
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<td>CGI</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>6.5 (0.6)</td>
<td>6.5 (0.6)</td>
<td>6.3 (0.6)</td>
<td>6.7 (0.6)</td>
<td>4.008</td>
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<td>3 months</td>
<td>3.1 (1.7)</td>
<td>3.1 (2.0)</td>
<td>3.4 (1.5)</td>
<td>2.9 (1.6)</td>
<td>1.026</td>
<td>0.361</td>
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<td>-3.4 (1.9)</td>
<td>-3.0 (1.6)</td>
<td>-3.7 (1.6)</td>
<td>2.901</td>
<td>0.058</td>
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<td>3-months change from baselinea</td>
<td>-3.4 (0.2)</td>
<td>-3.1 (0.2)</td>
<td>-3.6 (0.2)</td>
<td>1.613 (0.2)</td>
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<td>BPRS</td>
<td>64.9 (13.3)</td>
<td>64.3 (12.9)</td>
<td>61.6 (12.8)</td>
<td>67.8 (13.5)</td>
<td>3.411</td>
<td>0.035</td>
</tr>
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<td>Baseline</td>
<td>35.3 (11.7)</td>
<td>35.9 (13.9)</td>
<td>37.1 (10.9)</td>
<td>33.5 (10.5)</td>
<td>1.554</td>
<td>0.214</td>
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<td>3 months</td>
<td>29.7 (15.8)</td>
<td>28.4 (14.4)</td>
<td>24.5 (16.0)</td>
<td>-34.3 (15.5)</td>
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<td></td>
</tr>
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<td>3-month change from baseline</td>
<td>28.9 (1.6)</td>
<td>-27.1 (1.6)</td>
<td>-32.1 (1.4)</td>
<td>2.894 (0.058)</td>
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<tr>
<td>BPRS</td>
<td>4.4 (5.4)</td>
<td>3.6 (4.7)</td>
<td>3.7 (4.6)</td>
<td>5.6 (6.2)</td>
<td>2.732</td>
<td>0.068</td>
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<tr>
<td>Baseline</td>
<td>4.2 (4.5)</td>
<td>3.3 (4.6)</td>
<td>4.5 (4.0)</td>
<td>4.6 (4.6)</td>
<td>1.493</td>
<td>0.228</td>
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<td>3 months</td>
<td>-0.2 (5.4)</td>
<td>-0.3 (4.0)</td>
<td>0.9 (5.1)</td>
<td>-1.0 (6.2)</td>
<td>1.828</td>
<td>0.164</td>
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<td>3-month change from baseline</td>
<td>0.9 (0.6)</td>
<td>0.4 (0.6)</td>
<td>-0.2 (0.5)</td>
<td>1.197 (0.305)</td>
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<td>3-month change from baselinea</td>
<td>0.9 (0.6)</td>
<td>0.3 (0.6)</td>
<td>-0.2 (0.5)</td>
<td>1.173 (0.312)</td>
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<td>SANS</td>
<td>14.2 (4.3)</td>
<td>14.4 (4.3)</td>
<td>13.7 (4.2)</td>
<td>14.4 (4.5)</td>
<td>0.443</td>
<td>0.643</td>
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<td>2.6 (4.2)</td>
<td>3.6 (5.7)</td>
<td>2.7 (3.2)</td>
<td>1.8 (3.3)</td>
<td>2.772</td>
<td>0.065</td>
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<td>3 months</td>
<td>-11.6 (5.6)</td>
<td>-10.8 (6.8)</td>
<td>-11.0 (5.2)</td>
<td>-12.6 (4.9)</td>
<td>1.946</td>
<td>0.146</td>
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<tr>
<td>3-month change from baseline</td>
<td>10.6 (0.6)</td>
<td>-11.4 (0.6)</td>
<td>-12.4 (0.5)</td>
<td>2.846 (0.061)</td>
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<tr>
<td>CDSS</td>
<td>2.6 (3.6)</td>
<td>2.3 (3.1)</td>
<td>2.2 (3.6)</td>
<td>3.2 (3.9)</td>
<td>1.387</td>
<td>0.253</td>
</tr>
<tr>
<td>Baseline</td>
<td>1.9 (3.4)</td>
<td>1.6 (3.3)</td>
<td>2.9 (4.1)</td>
<td>1.4 (2.7)</td>
<td>3.500</td>
<td>0.032</td>
</tr>
<tr>
<td>3 months</td>
<td>-1.7 (4.5)</td>
<td>-0.7 (4.1)</td>
<td>0.7 (4.7)</td>
<td>-1.8 (4.3)</td>
<td>5.076</td>
<td>0.007</td>
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<tr>
<td>3-month change from baseline</td>
<td>0.9 (0.5)</td>
<td>0.4 (0.4)</td>
<td>-1.4 (0.4)</td>
<td>4.404 (0.014)</td>
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<tr>
<td>YMRS</td>
<td>12.0 (5.4)</td>
<td>12.8 (6.5)</td>
<td>11.8 (4.6)</td>
<td>11.7 (5.2)</td>
<td>0.763</td>
<td>0.468</td>
</tr>
<tr>
<td>Baseline</td>
<td>2.5 (3.6)</td>
<td>2.9 (3.8)</td>
<td>3.0 (3.8)</td>
<td>1.9 (3.1)</td>
<td>1.787</td>
<td>0.171</td>
</tr>
<tr>
<td>3 months</td>
<td>-9.5 (5.9)</td>
<td>-9.9 (7.1)</td>
<td>-8.8 (5.0)</td>
<td>-9.8 (5.6)</td>
<td>0.602</td>
<td>0.549</td>
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<tr>
<td>3-month change from baseline</td>
<td>-9.2 (0.5)</td>
<td>-9.0 (0.5)</td>
<td>-10.1 (0.4)</td>
<td>1.627 (0.200)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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.

b Controlling by baseline SANS and CDSS total scores.
3.3.2.2. Adverse events. Intention-to-treat analyses revealed that Quetiapine showed a marked increase in the prevalence of treatment-emergent somnolence (Quetiapine 34.0%; Ziprasidone 15.4%; and Aripiprazole 16.7%) ($\chi^2 = 6.827; p = 0.033$) and an increased duration of sleep (Quetiapine 12.0%; Ziprasidone 3.8%; and Aripiprazol 14.0%) ($\chi^2 = 7.040; p = 0.03$). Significant differences were also found in the frequency of body weight increase between treatments ($\chi^2 = 11.551; p = 0.003$). One individual on Ziprasidone (1.6%) showed a body weight increase compared to 23.6% of patients on Aripiprazole and 14.0% of patients on Quetiapine.

3.3.3. Concomitant medication use

Patients on Quetiapine were taking significantly less hypnotics (lormetazepam) at the three month assessment compared to those patients on Aripiprazole and Ziprasidone (12.0% Quetiapine; 32.7% Ziprasidone and 22.2% Aripiprazole; $\chi^2 = 6.279; p = 0.043$). No significant differences were found between groups in the rate of antimuscarinic agents, benzodiazepines, mood stabilizers and antidepresant use at 3 months (data available upon request).

4. Discussion

Aripiprazole and Ziprasidone have demonstrated significantly higher effectiveness (lower discontinuation rate) than Quetiapine in the treatment of first-episode patients at 3 months. Insufficient efficacy in the group of Quetiapine is the main reason for the discontinuation rate differences between antipsychotics. Consistently, Quetiapine was less efficacious than Aripiprazole and Ziprasidone in reducing positive symptoms and showed the lower rate of responders. Only Ziprasidone was demonstrated to be less effective than Quetiapine and Aripiprazole in improving depressive symptoms. Overall, no treatment advantages in reducing the severity of global, manic and negative symptomatology were found between the three SGAs. The profile of side-effects varied between treatments.

4.1. Effectiveness

Treatment discontinuation rate during the acute treatment of first-episode patients was significantly greater in patients given Quetiapine (61.3%), mainly due to insufficient efficacy. Accordingly, a lower rate of responders was found in the Quetiapine group. A higher risk of treatment discontinuation during the acute phase of treatment has been also observed in Quetiapine-treated patients (Crespo-Facorro et al., 2013). Effectiveness studies using standard dosage ranges pointed out that Quetiapine may be somewhat less effective than some other SGAs (Sprattshatt et al., 2011). The best available evidence from trials suggests that most people who start Quetiapine stop taking it within a few weeks (Komossa et al., 2009). Inadequate and transient dopamine 2 receptor occupancy with Quetiapine may lead to insufficient antipsychotic efficacy (Tauscher-Wisniewski et al., 2002). However, medium-term randomized studies in first-episode have shown similar rates of all-cause treatment discontinuation in first-episode patients treated with Quetiapine compared to other SGAs (McEvoy et al., 2007; Kahn et al., 2008). Kahn et al. (2008) described no difference between Quetiapine and Ziprasidone in the rate of treatment discontinuation for any cause, although discontinuation because of insufficient efficacy was higher to some extent in Quetiapine (40%) compared with Ziprasidone (26%) at 1 year. In a sponsored investigation, McEvoy et al. (2007) observed no significant differences between Olanzapine, Risperidone and Quetiapine in clinical efficacy and the rate of treatment discontinuation after 1 year. Variations emerged regarding specific short- and mid-term safety profiles and the clinical efficacy of individual antipsychotics may account for discrepancies in effectiveness between studies (Glick et al., 2011). Lengthy follow-up studies are required to determine whether these differences in effectiveness observed during short-term treatment remain in the latter phases of treatment.

Depressive symptoms improvement, as measured by the CDSS, differed between treatments, with the biggest advantage seen with Quetiapine and Aripiprazole. Open-label trials had pointed out that Quetiapine may be a useful agent in the management of depressive symptoms in individuals with psychosis (Sajatovic et al., 2002; Lee et al., 2009). In previous first-episode studies, there were no significant differences between SGAs (including Quetiapine) in reducing depressive symptoms after 1 year of treatment (McEvoy et al., 2007; Kanh et al., 2008). No notable changes of negative symptoms were found with any of the three antipsychotics.

4.2. Side-effects and concomitant medications

The differences in the percentage of patients with treatment-emergent parkinsonism (Aripiprazole = 13.9%; Ziprasidone = 15.4% and Quetiapine 4.0%) and akathisia (Aripiprazole: 25.0%, Ziprasidone: 25.0% and Quetiapine: 8.0%) may be of clinical interest. A higher percentage of extrapyramidal 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., 2013). A higher incidence of akathisia early after Aripiprazole treatment was initiated has been previously reported (Kerwin et al., 2007). Likewise, in first-episode patients, a higher incidence of parkinsonism (16%) and akathisia (28%) in the Ziprasidone group has been found when compared to other SGAs (Kahn et al., 2008). Grootens et al. (2011) described that significantly more patients on Ziprasidone needed anti-muscarinic agents to relieve extrapyramidal symptoms compared to Olanzapine-treated patients with recent-onset schizophrenia.

Somnolence and increased duration of sleep was more prevalent in Quetiapine-treated patients. Significant differences were found in the frequency of body weight increase between treatments. Only one individual on Ziprasidone (1.6%) showed a rapid body weight gain compared to 23.6%Aripiprazole and 14.0% Quetiapine. A low propensity to induce weight gain has been related with Ziprasidone (Komossa et al., 2010). 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. As expected from the incidence of side-effects, patients on Quetiapine were taking significantly less hypnotic agents than Aripiprazole and Ziprasidone patients. In a recent review article, Quetiapine showed significantly less use of concomitant anti-Parkinson medication than Olanzapine, Risperidone, and Ziprasidone (Rummel-Kluge et al., 2012). Interestingly, the discontinuation rate due to severe or intolerable side-effects in our study was relatively low (9.9%) and does not seem to significantly affect medication compliance or treatment continuation at early phases.

4.3. Limitations

Our study has potential limitations that must be taken into account in the interpretation of the 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 favoring 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. Initial recommendations established a wide clinical dose range (150–750 mg/day) with a target dose of 400–600 mg/day, with a clear recommendation of reducing the dose by 30% in cases of first-episode (Small et al., 1997; Kasper et al., 2001). First-episode patients are more responsive and sensitive to side-effects. Young patients suffering from a first break of psychoses seem to be highly responsive to low doses of antipsychotics and more sensitive to extrapyramidal side effects and to acute weight gain (McEvoy et al., 1991; Basson et al., 2001). Based on previous
literature and clinical guides for treating FES patients, we decided to use a range of doses of 100–600 mg/day. More recent publications (McEvoy et al., 2007; Kahn et al., 2008) have reported similar mean doses of Quetiapine before discontinuation than in our study. Lately, various publications have suggested that higher doses than licensed are necessary for the therapeutic effect of Quetiapine, although no evidence supports this belief (Sparshatt et al., 2008). Controlled investigations have shown that the standard dosage range is appropriate in everyday clinical practice with no advantages of high-dosage (Johnsen and Jorgensen, 2008). 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. One additional limitation of this report may be the fact that multiple comparisons were made to explore clinical efficacy. However, we decided not to correct for multiple testing and thus, some of the significant associations we found could have been type I errors.

4.4. Conclusions

After a first episode of non-affective psychosis, Quetiapine-treated patients are more likely to discontinue treatment in the short-term due to insufficient efficacy compared to Aripiprazole and Ziprasidone patients. Establishing differences between SGAs may help clinicians with prescribing decisions for the treatment of individuals presenting with first-episode schizophrenia. Properly balancing the 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.

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The study, designed and directed by B-CF and JL-VB, satisfied current standards for research ethics and was approved by the local institutional review board.

Contributors

Benedicto Crespo-Facorro designed the study, collected clinical data, interpreted the results and drafted the manuscript. Victor Ortiz-Garcia de la Foz performed the statistical analyses and drafted the manuscript. Ignacio Mata interpreted the results and drafted the manuscript. Rosa Ayesa carried out clinical and cognitive assessments and reviewed the manuscript. Ema Valdizan helped in the interpretation of clinical data and reviewed the manuscript. Valdizan, E., Vazquez-Barquero, J.L., 2012. Long-term (3-year) effectiveness of haloperidol, risperidone and olanzapine for the acute treatment of first-episode non-affective psychosis. J. Clin. Psychiatry 63 (10), 1511–1521. Fengweidong, L., 2007. 0381B. Crespo-Facorro et al. / Schizophrenia Research 147 (2013) 375–382

References


Conflict of interest

Prof. Vazquez-Barquero has received honoraria for his participation as a speaker at educational events from Johnson & Johnson. Prof. Crespo-Facorro has received honoraria for his participation as a speaker at educational events from Pfizer, Bristol-Myers Squibb, and Johnson & Johnson that was deposited into research accounts at the University of Cantabria.

Mr. Valdizan, Mrs. Ayesa, Mrs. Suarez and Mr. Ortiz report no additional financial or other relationship relevant to the subject of this article.

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