Author’s response to reviews

Title: The switch from conventional to atypical antipsychotic treatment should not be based exclusively on the presence of cognitive deficits. A pilot study in individuals with schizophrenia.

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Author’s response to reviews: see over
Dear BMC Psychiatry Editorial Board Members,

Thank you very much for your prompt reply and the encouraging comments. We have revised our manuscript in accordance with the suggestions of both referees (see our detailed responses below), and are returning the new version, for your consideration as a Research article in your journal.

Sincerely, April 26th 2010

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RESPONSES TO REVIEWERS

We are grateful for the referees’ suggestions, which have been extremely helpful in improving the clarity and the scientific content of our manuscript.

Reviewer #1:

**Reviewer’s comment:** Given the small number of subjects in this study it should be regarded more as a pilot finding and although it supports recent larger trials the title of the paper (and the conclusions) might be altered to reflect this.

**Response:** The title of the article has been modified to reflect the commentary of the reviewer: “The switch from conventional to atypical antipsychotic treatment should not be based exclusively on the presence of cognitive deficits. A pilot study in individuals with schizophrenia”.

The conclusions of the article have also been modified to reflect this limitation of the study. We have now included the suggested observation in the 2nd paragraph of conclusions, page 14: ……”Bearing in mind that results from the present study lack of a representative sample of patients, however this pilot finding is consistent with recent literature in which atypical APD do not demonstrate apparent beneficial cognitive effects compared to conventional APD”.

**Reviewer’s comment:** ….. Although the authors point out that they do not have a healthy control group it would be illuminating for the reader to know what are the expected norms for at least some of the tests for an age and gender matched control group. In this way it would be possible to judge the level of cognitive impairment in the patient groups.

**Response:** According to the reviewer’s suggestion, a comparison of the means on the performance on some of the tests with an age and years of education matched normal Spanish population has been added in the 2nd paragraph of results, page 9.
Reviewer's comment. It would appear that patients in the ‘typical’ group are somewhat disadvantaged compared to the ‘atypical’ group in that they have a slightly younger age at onset, more episodes of illness and therefore a longer duration of illness. Is there a potential ceiling effect here i.e., the longer the patients is ill the less likelihood there is of significant cognitive improvement?

Response. Although differences between the two groups of patients in the variables mentioned by the reviewer did not reach statistical significance, we might think that patients treated with typical antipsychotics could be more chronic and possibly less susceptible to cognitive remediation. In that case, cognitive enhancement in the patients treated with second generation antipsychotics would be easier to achieve. This cognitive improvement in the "atypical group" is not observed in our study. The “type of antipsychotic” factor does not seem to modify cognitive outcome. Nevertheless, other psychopharmacological and psychosocial strategies should be implemented to enhance cognitive outcome in schizophrenic patients. This last sentence has been added in the 2nd paragraph of conclusions, page 14.

Reviewer #2:

Reviewer's comment. This manuscript is correctly written, well performed, but suffers from the limits that were correctly underlined by the same authors: the sample is limited and the design is retrospective naturalistic. These two limits combined make the results, despite the adequate statistical analysis, difficult to be interpreted correctly because of very limited statistical power. For this reason sample should be largely increased.

Response. The reviewer underlines a major limitation of the study. That is the reason we have changed the title and conclusions of the article to indicate that the results of our pilot study converge with recent literature. To sum up, in long-term clinically stable schizophrenic patients treated with first generation antipsychotics, other cognitive enhancement strategies must be implemented as the switch to an atypical antipsychotic treatment probably will not change cognitive outcome.
**Reviewer’s comment.** Moreover drugs were divided into two large subgroups with a sort of hypothesized ‘class effect’ that is questionable, probably because of the naturalistic nature of the study and the limited numerosity of the sample. Again a larger sample should be analyzed.

**Response.** The reviewer correctly indicates the questionable separation of the two major families of antipsychotics. We decided to follow the traditional but still widely used distinction as it has exerted an important influence on modern psychiatric research. We agree with the reviewer on the need to reassess this classification as among second generation antipsychotics (equally among first generation) more than subtle psychopharmacological differences exist.

**Reviewer’s comment.** Size effect of changes should be calculated and analyzed to look if the statistically significant change, independently from the equivalence of treatments is also a clinically worth one.

**Response.** This observation raised by the reviewer is important as size effects for cognitive change are not homogeneous. Size effects for the cognitive variables for which performance significantly improved between T1 and T2 have been calculated and added to Results (Clinical and neurocognitive changes in all patients), 1st paragraph, and page 10. The clinical relevance of these results is explained in the discussion, 1st paragraph, page 11.

**Reviewer’s comment.** An unclear statistical fact is how PANSS score has been used as a covariate. In the text is said that PANSS scores are entered as a covariate in the repeated measures ANOVA, but is not clear what PANSS score: basal, final, both?

**Response.** PANSS positive scores and CPZ units at baseline were the only variables with significant statistical differences between the two groups. (See table 1). That was the reason why both variables were entered in that statistical model as covariates. Anyway, this was probably not well explained in the text. Modifications in the text are introduced in materials and methods, data analyses, 1st paragraph, page 8: “....As CPZ
units and PANSS positive scores at T1 were the only variables differing between the groups that reached statistical significance, they were entered as covariates in these analyses."...

**Reviewer’s comment** PANSS, again. I would prefer the change in PANSS score and if possible the change in the first 8 to 12 weeks of treatment: this is because a major decrease in psychopathology may result in better functioning and then in a better 'ecological' exercise of performances studied. This is somewhat considered in the discussion, but might be more clearly explained in the discussion. Against my comment is worth while to note that PANSS score did not change in a 'clinically significant' way in both groups, and in the basal assessment in both groups corresponds to a relatively stabilized clinical picture. So it seems that patients were already responders to treatment but it is not clear to what treatment: the same or another? If not this populations seems to be done in average by fairly responders already, stabilized by the new treatment.

**Response.** This is a very interesting suggestion since changes in PANSS are more probably to occur in the following weeks after the change of treatment in patients not stabilized. We think that this would be the objective of another kind of study (i.e. switching studies). It is true that characteristics of our samples correspond to patients previously stabilized by the ongoing treatment and in those cases cognitive improvement is less likely to occur. However, the main objective of this study is to confirm the superiority of atypical vs. typical antipsychotics on cognitive outcome in patients under long-term unchanged treatment. Anyway, to clarify this, the discussion has been modified in the discussion, 1st paragraph, page 12:“….Moreover, the characteristics of the sample in the present study corresponds to clinically stable, chronic patients, previously stabilized by the ongoing antipsychotic medication, so the effects of acute psychopathological changes on cognition, although not measured, are probably limited.”

**Reviewer’s comment.** It would bee useful, beside average dose, to compare the number of patients taking anticholinergics and benzodiazepines in the two groups.
Response. The variables benzodiazepines and anticholinergics dosages were entered in the analysis to assess their influence in cognitive outcome. Between groups comparison were not carried out due to the limited number of patients taking these medications. However, the information about the exact number of patients under these medications in each group has been added in results, general characteristics of patients, 1st paragraph, and page 9.