Author's response to reviews

Title: Compliance, persistence, costs and quality of life in young patients treated with antipsychotic drugs: results from the COMETA study

Authors:

Paolo A Cortesi (p.cortesi@campus.unimib.it)
Claudio Mencacci (cmencacci@interfree.it)
Ferrannini Luigi (Luigi.Ferrannini@asl3.liguria.it)
Elvezio Pirfo (dsm_g.maccacaro@aslt02.it)
Patrizia Berto (patrizia.berto@pbe.it)
Miriam CJM Sturkenboom (m.sturkenboom@erasmusmc.nl)
Fabiana L Lopes (flopes1@its.jnj.com)
Maria G Giustra (mgiustra@its.jnj.com)
Lorenzo G Mantovani (mantovani@unina.it)
Luciana Scalone (luciana.scalone@unimib.it)

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Author's response to reviews: see over
Dear Editor and Dear reviewers,

We are grateful for having the opportunity to improve manuscript entitled “Compliance, persistence, costs and quality of life in young patients treated with antipsychotic drugs: results from the COMETA study”, following the reviewers’ comments.

Although not all comments are fully answered according to the reviewers’ comments (in those case we specify our reasons), we have carefully considered all the comments received and adjusted the paper accordingly.

Our answers are reported in bold below each comment. The updated version of the paper containing all the adjustments made is attached.

Also, considering the opinions reported on the English language, the revised paper was submitted to language review by an English original language reviewer.

We hope that the paper can now be considered suitable for publication. If necessary, we remain willing to further adjust the paper for its acceptance.

Yours sincerely,

Lorenzo G Mantovani
Corresponding author
Faculty of Pharmacy
University of Naples Federico II – Naples (Italy)
email: mantovani@unina.it
Answers to comments by Douglas Faries

- Major Compulsory Revisions

Abstract:
1. Adding a key limitation – such as the lack of any comparator – would greatly enhance the understanding of the overall impact of this work. We have added this limitation in the discussion, together with other limitations and their implications. Compared with the other potential limitations we actually do not consider this as the most important one: as specified in the discussion, we actually did not aim to compare a difference, but rather to take a picture of the real-world burden and wellbeing of the target population, although we found trends that in our opinion are of interest. In any case, we are not sure about the feasibility, or even about ethical issues to preserve a totally unbiased comparison study in a real-world context, with the objectives of the COMETA study. However, as we cannot list, in the abstract, all the main limitations and their implications, we are afraid that only mentioning what the reviewer suggests would erroneously emphasize this aspect but not others that are actually relevant.

2. I think saying the focus on ‘young’ or naïve patients is stretched a bit by allowance of patients who have been treated for 10 years. I think we need to clarify the meaning of the terms used in the paper. We also adjusted the paper accordingly, to make them clearer to the reader. The two terms “young” and “naïve” actually refer to different aspects and criteria. First, all the patients involved in the study had to be diagnosed (and not treated) for ≤ 10 years. This criterion was related to the age of the patients, which is involved in the classification of “young” patients: we involved patients aged between 18 and 40 years, using criteria to define them that are consistent with those used in the literature. For instance, Cheng et al, (Psychological Medicine, 2011) involved patients aged 14-35 years. Braw et al (Schizophrenia Bulletin, 2008) involved young patients aged 18-35 years. Thorup et al (Social Psychiatry and Psychiatric Epidemiology, 2006) involved young adult patients aged 18-45 years. Instead, the term “naïve” refers to the duration of treatment, which is not necessarily related to the patients’ age of duration from diagnosis. In the literature we found few data and no standard criteria to be used [Hammer et al, 2011] for the identification of naïve patients. In our study, naïve patients were defined as those who at enrolment in the study were accessing the centre for the first time and who were starting a new treatment regimen (i.e., starting a new drug or a new dosage). Among the enrolled patients, who were all selected for being young, a subgroup of naïve patients was identified and analysed separately.

Introduction:
3. I believe there is relevant literature that has not been discussed. For instance, there is literature on early intervention in the prodromal stage of schizophrenia that is starting to address earlier treatment. A more thorough review would be beneficial.

Thanks to your comments, we have understood that speaking of early intervention in this paper can be misleading. Hence, we have deleted the paragraph focusing on early intervention and added references of very recently published studies on costs in schizophrenia (Sarlon et al, 2012; Zeidler et al, 2012 and others)

General:
4. In several places the descriptions of the work are quite lengthy and the key points could be delivered much more succinctly. In particular, the methods section (details on the scale) and the results section (often merely restating numbers already in the tables/figures) could be shortened substantially.

As regards methods, we have slightly reduced the description of clinical scales, assuming that details omitted are probably known by the target readers, but not relevant for this study. However, we assume that not all readers know the information necessary to understand and interpret the estimates obtained with the different scales/computations, hence we have left details particularly on the HRQoL instruments and on cost estimates.

However, we have canceled from the text the results that are shown in the tables and only report those not specified in the tables. We hope that the manuscript is improved now.

Methods:
5. I would not refer to this as an ‘ambispective (both retrospective and prospective) study. I consider this a prospective study. Many observational prospective studies ask information on the recent past to establish a baseline. I do not view this as any different here.

The overall target observational period includes 3 months before (retrospective) and 12 months after the enrolment (prospective), with 3 months pre-enrolment actually corresponding to ¼ (i.e., not so short compared with the prospective period) of the post-enrolment observational period. Some studies, generally for economic or time reasons, only consider the retrospective period (less costly and less time consuming studies), others can be only prospective, i.e., observe the subjects starting from the time of enrolment. With this study, we aimed to merge the advantages of a retrospective period with those of a prospective period: hence, we collected data on the past + present (3 months before enrolment) and on the future (around 12 months). This allowed us to make our estimates considering a mean observational period of 11.4 + 3 = 14.4 months per patient. This latter detail answers point number 12.

Results:
6. The potential impact of dropouts is not taken into account anywhere. For instance, if patients who dropped out were more likely to have poor outcomes, switch or stop medications (as one might expect), then this could impact the outcomes. As an
example, it would not take much confounding from missing data to change the “decrease” in idle patients to be a real increase.
For the longitudinal analyses, utilizing a longitudinal statistical model that accounts for within patient correlations can at least partially address this missing data issue.

Only 7.8% of the patients were not observed for the entire study period, for different reasons, also specified in the current version of the paper (results, sample description section): 39 patients (6.1%) asked their clinician to withdraw from the study, 5 had reasons not allowing them to remain in the study (pregnancy, death, severe adverse event), 5 (0.8%) moved to a different city or different care centre, and 1 patient was lost to follow-up.

We do not have elements to consider the reason for discontinuation related with the participants’ health or outcomes in at least most of the patients who interrupted participation in the study. The 39 patients who asked the physician to withdraw from the study may have had some reasons related to the task of completing the questionnaires submitted during the data collection. Only a few patients might have had some reasons of discontinuation related to their outcomes: those moving to another centre, or the one that was lost to follow up. However, they were too few to investigate any possible relationships with their outcomes. However, we do not believe that the results could be biased by the discontinuation of these few patients. Furthermore, the longitudinal analyses we performed to answer the other comments gave us results that are almost identical to those we reported in the previous version of the paper.

Finally, we also compared all the characteristics at baseline (socio-demographic, clinical, HRQOL) reported in table 1 and 2, between patients who completed the study and those who discontinued and we did not find any difference that should be noted considering the reviewer’s comment. We have added a statement on this in the paper (results, sample description section).

7. At one point the subset of naïve patients is singled out. Based on the introduction, I would have expected the focus to be on patients who were more newly diagnoses (to focus on early intervention). However, this focuses on patients initiating new therapy. What was the justification of this instead of focusing on early initiation as the introduction suggested?

We particularly thank the reviewer for this comment. Actually, although the “naïve” patients who participated in the study were likely to be involved in early treatment, no specific criteria were established on this. Furthermore, only the minority of the study sample could be identified as naïve patients. Accordingly, we deleted the paragraph focusing on early intervention to avoid misleading messages, and adjusted some statements so that they can clarify the added value of this study (introduction and discussion).
Moreover, we have added two paragraphs in the abstract (methods and results) and one in the discussion on the comparison between naïve and non naïve “While no significantly different direct costs were found between naïve and non naïve patients, naïve patients showed generally a significant mean higher improvement of clinical outcomes, HRQoL and indirect costs, compared to the others. However, the study sample was probably not suitable to obtain reliable results from these comparisons.”

8. If a subset of patients is truly of interest, then understanding other baseline differences between the subgroups is important – as these are not randomized groups and biases are present. For instance, is it the fact that the patientis ‘ naïve’ or would all patients with severe scores at baseline respond the same way?
As specified in the discussion, this study did not aim to demonstrate any difference, but rather to estimate the socio-economic impact of the target condition, according to real-world clinical and treatment aspects. Accordingly, we did not have any need, or it would even have been non ethical to randomize the group to clinical practice versus no treatment. However, some biases could be present and have been clarified in the discussion. Furthermore, in table 1 and 2 we report the comparison between naïve and non naïve patients at baseline, hence other differences found during the observational period.

Discussion:
9. There are several important limitations that should be discussed. First, this is an uncontrolled study. Thus, the first statement in the Conclusions needs to be interpreted in the light of this fact. We cannot prove from this data that early treatment is the best option. Second, this study was conducted in a single country and may or may not be generalizable into other systems with different costs and resource use structures. Third, analyses did not attempt to account for missing data or any other potential biases – only summary statistics are presented.

The “limitations” paragraph has been updated. Please note that we do not specify anything about early treatment and missing data here because: the detail on early treatment has been removed as actually we did not have suitable data on this; the detail on the few missing data is clarified in the results section as solved. We focussed the discussion and the limitations paragraph on aspects that we consider potentially relevant to be considered when interpreting/using the results. Furthermore, we have added a paragraph on the external validity of the results: “To expand applicability of our results, among the results we specify the mean consumption of specific categories of resources, which could be multiplied by different unit costs that are applicable in other health care systems.”

- Minor Essential Revision
10. General: Authors should comment on the ‘usual care’ nature of the study given the fixed visit schedule and collection of many scales that are not a part of usual care. We understand that by “usual care” the reviewer refers to the specification “according to clinical practice” given in regard to the frequency of the examinations that were fixed for data collection. We actually meant to specify
that the patients could undergo each examination within a time range of +2 weeks from the fixed date, so as to manage it more consistently with those that were likely established according to clinical practice. We understand that this detail is misleading and have changed it with a hopefully clearer sentence.

11. General: It was not clear to me if a requirement of the study was that the patient was initiating an antipsychotic treatment at baseline. This needs to be clarified

The requirement was that the patients had to be in treatment with antipsychotic drugs at enrolment, either started previously or started at the time of enrolment (see sentence in subjects and procedures section).

12. Results: The patient observation time that is mentioned (14.4 months) is somewhat misleading to me as only 11.4 months were really observed (prospectively). Similarly, I found the averaged days free from symptom relapse (460.2) not interpretable without having the total number of days. “During follow up, 109 patients, 17.1% of the study sample, had symptoms relapses. On average 460.2 (SD= 5.7) days/patient free from symptom relapse was recorded. ”

As regards the first point, we observed the patients for both 3 months before and for around 12 months after enrolment (see also answer to question 5) – hence, we consider it more appropriate to report the amount of the total observational period. The fact that part of the observational period was retrospective does not compromise its validity as a real observational period, although it may somewhat reduce the precision of the data collected. However, we paid attention in choosing a not too long time period to minimize recall biases.

As regards the second point, we were able to analyze data on relapses from both the retrospective and prospective periods, which reached the maximum amount of 544.2 of days of observation, or 17.9 months, as specified at page 10.

13. Results: The text comparing the pre and follow up period resource use is a bit confusing to me. First, we have different periods of time. Second, the enrollment criteria has an influence on the baseline period.

As regards the first point, although different periods of time were used between subsequent examinations, all costs were reported as mean € (or days) per patient per month, hence the results are comparable to each other. A clarifying sentence has been added in the methods section, when we specify how results on costs are reported: “The use of mean per patient-month makes it possible to adjust the results for the different periods of time between the examinations when the data were collected”. The second point, on the influence of the selection criteria on results, is clarified in the results section. Furthermore, we point out this possible influence in the discussion now.

14. Results: There is a statement saying the quota payed by the patient was on average ‘null’. If any one patient had a positive value then the average cannot be zero.

The text has been amended: the quota paid by most of the patients was null.
15. Tables: Adding the N’s to the columns of tables such as Table 3 and 5 would be very beneficial.

N’s added
Answers to comments by: Jan Volavka

Reviewer's report:

Major compulsory revisions

1/ In the Subjects and Procedures section, the authors state that patients who were “drug addicted” were ineligible. It is necessary to explain what criteria were used to define “drug addiction”. Furthermore, it is not clear if this includes alcohol use disorders.

This detail was not complete and has been amended in the paper: patients were excluded if at enrolment in the study they were attending a centre specialized for assisting and treating subjects addicted to drugs or alcohol.

2/ The project used 86 participating centers, and an unknown (but obviously large) number of raters administering various assessment instruments. Was there any attempt to determine interrater reliability, for example, for the PANSS scale, and for other instruments? How were the raters trained?

The centres participated in two kick-off meetings before the study started, within a 3 year long educational program in which the raters (clinicians) were trained for the completion of all the instruments used in the project (now added in the first paragraph of the methods, assessments section). The possible interrater variability was not measured.

3/ “Persistence with the antipsychotic drug treatment was estimated by means of Kaplan-Meier curves, by comparing the mean number of patient-days (i.e. number of days each patient persisted in each treatment) of permanence in the same drug class (i.e. class of atypical, typical, combination of both classes, or no antipsychotic drug)” (Stat section).

This is an unusual method of defining persistence. With this method, it was possible for a patient to switch for example from risperidone to olanzapine and then to clozapine and he would still be considered persistent since all 3 switches occurred within the same class (atypicals). This method may explain, in part, the unusually high persistence rate for the atypicals depicted in Fig 3. Such results are of course not comparable with those obtained using in other studies (e.g. the CATIE) that counted each switch as a discontinuation, no matter what the patient was switched to. This problem should be explained in the Discussion section.

The CATIE study was a double-blind RCT aimed at comparing the effectiveness of antipsychotic drugs, using 4 drugs at predefined doses. In a more recent study (Guo et al, 2011), which was instead a naturalistic one, the authors aimed at measuring the cognitive effects of antipsychotic drugs involving only patients using one among 7 drugs. Both these studies, and probably other studies, limited their observations to selected samples of patients who met specific criteria for treatment.

In order to obtain a more complete real-world picture of our target population, we did not impose these criteria in regard to the treatment followed during the
observational period; hence the patients were recruited regardless of their treatment before and after enrolment in the study. As a consequence, we enrolled patients that had many different combinations of many different antipsychotic drugs (18 drugs were taken in total, see figure 1). Detailed knowledge on switches between different molecules, or even between different dosages, would have been too difficult and not really informative. In order to provide a relatively complete and clear description and measure of the persistence with antipsychotic treatment, we decided to adopt the approach shown in figures 2 and 3, which focuses on classes of drugs. This approach is not common, but useful to show the natural complexity of a treatment pattern (as an example it has also been used in hypertension, see Mazzaglia, Mantovani, Sturkenboom et al, Journal of Hypertension, 2005). However, this approach makes it possible to show conservative results, since it shows the complexity of treatment considering only classes of drugs, and suggests a much higher complexity than is relevant for the treatment decisions and consequences in this area.

4/ In the Background section, we read that “The aim of this study was to assess compliance and attitude toward antipsychotic drug treatment, persistence and clinical status and Health-Related-Quality-of-Life (HRQoL)…”.

In view of that aim, it is puzzling that the authors limit the data presentation for these variables to displays of averages in Figures 4-6. Without appropriate testing, we do not know which, if any, of these “trends” achieve statistical significance. These tests should be done, and the presence or absence of stat. significance should be reported in the text and reflected in the Abstract. The current Abstract states that “the attitude toward treatment improved”. This statement which implies an unequivocal effect is misleading in view of the minimal change observed. In any event, measures of dispersion around the means must be provided.

The results are now reported in one table (while figures are removed), containing both means and SD, plus the results of the statistical analyses for repeated measures.

Discretionary revisions

1/ I would replace Figures 4-6 with a table that would give means, standard deviations, and significance levels for each of the time effects (“trends”) (after appropriate corrections for multiple testing).

The results are now reported in one table (while figures are removed), containing means and SD, plus the results of the statistical analyses for repeated measures. Both results on the full sample and those on comparing naive and non naive patients are specified. Results are corrected for multiple testing according to Bonferroni.

2/ I would omit the Conclusions section. As it is, it consists of general statements such as “How patients with schizophrenia are treated can have important repercussions…”.

These statements are true, but not new. Furthermore, they do not follow in any clear way from the currently presented data.
The discussion has been revised according to the reviewers’ comments and the conclusion adjusted.