Author’s response to reviews

Title: Monitoring patients on chronic treatment with antidepressants between 2003 and 2011: Analysis of factors associated with compliance

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Version: 1 Date: 28 Sep 2015

Author’s response to reviews:

Dear Dr Charlson

BMC Public Health

Following your indications regarding our manuscript entitled “Monitoring patients on chronic treatment with antidepressants between 2003 and 2011: Analysis of factors associated with compliance” (PUBH-D-15-00303) we have now addressed the reviewers’ comments and concerns.

We thank the reviewers for their comments, which have helped to improve the clarity and the quality of our paper.

Please find below our responses to the points they raised and a discussion of the changes we have made following their recommendations.

Changes in the manuscript have been highlighted.

Please note that, as requested, novel references have been added (2, 3, 4, 7, 9,19, 20); this means that all the reference have moved, but are not coloured.

Yours sincerely,

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Reviewer's report:

Reviewer #1: Medication adherence in mental disorders, and factors associated with improved adherence, are an important area of research and one for which there is surprisingly little data available. The manuscript is well written, and in particular the authors do a good job of addressing limitations of the data in the Discussion. A number of suggestions are provided below that should serve to strengthen the paper further.

Major comments:

1. Please check the information you report against your references. The Murray (2012) paper does not report an increased prevalence of depression; whilst absolute number of DALYs may have increased, the population prevalence has not changed. The appropriate reference for this would be Ferrari, 2013. There is also a more recent review on prevalence of anxiety disorders, see Baxter, 2013. Both references are provided below.

-We agree with this suggestion and we have included two relevant references in the introduction section:

“Although the prevalence of depression has not increased over time (2), depressive disorders account for 40.5% of the disability-adjusted life years caused by mental illness (3). The global current prevalence of anxiety disorders is 7.3%, ranging from 5.3% in African cultures to 10.4% in Euro/Anglo cultures (4).”

2. The current description of guidelines for anxiety disorder treatment is overly simplistic. I suggest you look carefully at the NICE Quality Standard [QS53] for treatment of Anxiety Disorders (published Feb 2014). This states that the preferred first line of treatment should be evidence-based psychological interventions (https://www.nice.org.uk/guidance QS53/chapter/Quality-statement-2-Psychological-interventions). You can then justify your focus on pharmaceutical interventions within the context of the stepped-care approach advocated by the NICE guidelines, and perhaps clarify why anti-depressants are recommended instead of anti-anxiety medications.

-Thank you for the suggestion. We have included the NICE guidelines and their recommendations in the introduction, in our discussion of the interventions:
“The NICE guidelines recommend psychological interventions as the first line of treatment, rather than pharmacological treatment. Pharmacological treatment is indicated as a later additional step in the case of non-response to psychotherapy. The use of antidepressants is one of the standard treatments for anxiety disorders, due to the significant improvements obtained in quality of life and functional disability. The routine use of benzodiazepines should be avoided because they are associated with tolerance and dependence, and antipsychotics are associated with a number of adverse effects (7) (Bee Wee, 2014).”

Minor comments:

>3. The first 2 paragraphs of the Introduction could be condensed into a single more succinct paragraph.

- We have deleted the following part of the introduction:

"Anxiety is a psychiatric disorder that is most often attended by primary care physicians, and accounts for between 9% and 19.5% of patients attending primary care services (3). As for depression, it is one of the most common psychiatric disorders and a major cause of disability and suicide (4)."

>4. The first 2 sentences of paragraph 4, commencing "Depression presents high rates of relapse....." need references.

- Thank you, we have now included the reference to Kessler:


>5. I found the Methods section very clearly presented. But I wonder if you could add a brief explanation of the reason for the exclusion criteria around patients receiving amitriptyline?

- The main reason is the generalized use of amitriptyline as adjunctive therapy for neuropathic pain and the possible increase in compliance in these cases. In fact the incidence is low (n = 317). We now include this information in the exclusion criteria.

>Is there a reference available for the WHO Centre for Statistics Methodology cited under 'Definition of compliance with treatment'?

- We have included two references to the Daily Dose defined by the WHO, and to the definition of compliance with treatment:


>6. It seems there is text missing from the paragraph describing the logistic regression models?
- We have extended the statistical analysis section to include the method used to select the variables:

“Statistical analysis: A descriptive analysis was performed of the cohort considering frequencies and percentages. The compliance rate was estimated with a confidence interval of 95% using normal approximation. To determine its possible association with other variables, the compliance rate was described and the Chi-square significance test was performed. Crude and Adjusted odds ratios (OR) of compliance with treatment were estimated by multivariable logistical regression models. The complete model and a second model with variables that showed statistical significance, two logistic models (Enter method) were adjusted. The Hosmer-Lemeshow test and area under the curve ROC (AUC) were computed to evaluate the performance of the multivariable models. P values less than 0.05 were considered statistically significant”.

>7. This might seem a bit picky, but the terms 'adherence' and 'compliance' seem to be used interchangeably. I'd suggest you choose one term and use it consistently throughout (including Tables and in the Discussion).

- We have replaced the term “adherence” with “compliance” throughout the manuscript

References:


Reviewer 2:

>-Abstract
>-Absolute numbers are helpful. Please provide details for men and women separately.

-Thank you for the suggestion: Compliance rates are now presented separately for men and women in the Abstract section.
- Please define “industrialized countries”
- The authors of reference 1 define these countries as “more economically developed”. We now use this term in the first paragraph.

> Maybe you can update your information about DALYS associated with depression and anxiety?

- The burden of mental and substance use disorders increased by 37.6% between 1990 and 2010. In most disorders the rise was driven by population growth and ageing.

We have updated the information with the following reference:


- Clinical practice guidelines differ between countries. Do you refer to Spain? Are further clinical guidelines available?

- A variety of guides and classifications are used:


  *OMS. Décima Revisión de la Clasificación Internacional de Enfermedades CIE-10. Trastornos mentales y del comportamiento. Madrid: Meditor; 1992


The last guidelines to be published in Spain were the following:

- Grupo de Trabajo de la Guía de Práctica Clínica sobre el Manejo de la Depresión Mayor en el Adulto. Guía de Práctica Clínica sobre el Manejo de la Depresión Mayor en el Adulto. Ministerio de Sanidad, Servicios Sociales e Igualdad. Agencia de Evaluación de Tecnologías Sanitarias de Galicia (avalia-t); 2014. Guías de Práctica Clínica en el SNS: avalia-t 2013/06.
In the introduction we now mention the recommendations of the NICE guidelines (Bee Wee, 2014).

> What are the potential side effects for treating depression with antidepressants? Can you distinguish between men and women?

- The most frequently experienced known side effects of antidepressants were libido decrease, tiredness, feeling drowsy, insomnia, emotional flatness, sweating, a dry mouth, gastrointestinal complaints, and decreased erection or ejaculation.

Knowing patients’ perceptions of antidepressants and their experiences with their use may therefore help to explain their refusal to take a prescribed medicine, although we did not study the side effects associated with non-compliance.

> Might it be possible to mention limitations of using registry data to answer the question of medication adherence?

- We agree; we now mention the use of registry data in the limitations section.

> Methods

> Is it possible to describe the sociodemographic variables of the cohort?

- We have included a short description of the cohort in the methods section:

The sample comprised 3684 subjects (26.8% males and 73.2% females with a mean age of 53.7 years (sd=17.8).

> Might it be possible to explain why this definition of compliance with treatment was chosen?

- The majority of studies evaluating compliance have assessed the percentage of correct medication intake or sufficient medication refills to infer a compliance of at least 80% during 6 months of treatment with pharmacy records or computerized administrative databases.

In the methods section we now include our main reference for establishing the criterion of compliance:


> Do you have any information about psychotherapy use?
We do not have data on psychotherapy use in our study or in our environment. In the introduction we include the NICE guidelines’ recommendations regarding psychological interventions.

Results

> Please describe the gender distribution of the sample. Please describe similarities and differences in sociodemographic variables compared to the general population in Lleida.

Women accounted for 73.2% of our sample of subjects receiving antidepressive treatment. In contrast, in the general population in Lleida (309,786 inhabitants) 48.2% were women, with a mean age of 42.0 years (SD:23.9).

We have now added this information in the first paragraph in the results section.

-Do you refer to “sex” or to “gender”?

Affiliation data and the classification as female or male were made according to the corresponding information in the Primary care information system. We now use the term “gender” throughout the manuscript.

> Is there any possibility to investigate the association between seriousness of depression and adherence to medication?

-Although depression severity may be a relevant factor in analysing compliance with antidepressive treatment, we were not able to study this relationship because the data registry did not allow its analysis.

> Can you please describe age difference in adherence?

-Compliance in the >65 age group was 26.6%; in the< 35 age group it was 14.6%. These results are presented and expanded upon in relation to other variables analysed in table 2.

> I would be very much interested to know more about the funding schemes in Spain. This might be of critical interest for readers who are not familiar with the Spanisch funding systems.

-In Spain, the public health system guarantees access and partial pharmacy coverage for all residents registered in the census (1). Nonetheless, we hypothesized that the more vulnerable groups would have greater difficulties in complying with treatment and would be at a higher risk of treatment failure than the non-vulnerable groups.


> Overall comments
Please provide not only percentages but absolute numbers as well. Please report always gender specific and of possible age specific rates and numbers.

-Thank you very much for the suggestion. In the new version we have included the percentages for compliance both globally nd separated according to gender, corresponding to Table 2. We also include the absolute numbers of all categories of variables.

> The limitations section needs a description of the methodological limitations of this kind of studies based on routine data. The discussion could be shortened but the methodological constrints would need clear information.

-Thank you. We have described other limitations arising from the lack of information on this type of study:

"Among the limitations of studies of this kind based on routine data is the lack of information about cultural and social factors and patients’ opinions which also have an important bearing on the analysis of compliance".