Reviewer's report

Title: Clinical and Economic Consequences of Long-Term Use of Benzodiazepines in Patients with Generalized Anxiety Disorder

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Reviewer: Antoine Pariente

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Manuscript

Clinical and Economic Consequences of Long-Term use of Benzodiazepines in Patients with General Anxiety Disorders

REVIEW

General comment:
The question investigated is interesting and the datasource used valuable. However, the methods retained do not allow fully achieving the objective. In their current presentation, the results do not fully sustain the discussion and the conclusion, and the title is a bit misleading. The reason for this is that, if the authors quite adequately evaluate the evolution of the costs after benzodiazepine initiation, they design they chose do not allow determining whether the increase is related to:

- some side-costs induced by benzodiazepine adverse effects,
- the consideration of a new disease in patient management: 75% of subjects use benzodiazepine in monotherapy for their GAD, without other treatment in the preceding 6 months. Thus for these patients, the GAD could be incident, with no cost related to the GAD in the prior 6 months, and costs related to it only after treatment initiation)
- the natural trends of costs in patients

I was very interested in the costs evaluation, but the methods have to be revised (and the paper accordingly) if the authors want to pursue the objective of evaluating the potential consequences of benzodiazepine prescriptions. For this, they have to compare at least with another cost evolution, for instance that following introduction of SRIs in patients with GAD. Although there would be some limitations in such comparison (cost-increase benzo monotherapy vs. SRI monotherapy; eventually add-on benzodiazepine vs. add-on SRI), this would give information on trends of cost in patients being put under treatment for GAD.

Major Compulsory Revisions

I. Data
The used data are quite old (last benzo initiation in 12/2007). It is not sure
whether the cost estimation made is still valid. Do the author have the opportunity to update the data?

II. Study design
1. As indicated in the general comment, qualifying cost increases as economic consequences of long-term use of benzodiazepines (title, objective stated at the end of introduction section (impact), conclusion section of the discussion) cannot be done without providing a reference for cost evolution and comparing cost-evolution under benzodiazepines with this reference. Methods do not allow achieving the objective currently, which is pitifully as the cost estimations seem to have been performed quite appropriately. It is necessary that the authors either change the methods to achieve the objective (which is interesting) or lower their ambition to simply evaluate the “evolution of healthcare cost following benzodiazepine initiation in GAD patients” (which would be of less interest). This change in methods would need to use data not included in the present analysis, but these are available from the datasource the authors used.

2. It is necessary to clearly precise that pre and post-index periods had both 6-month lengths. I did not find it clearly stated in the manuscript.

III. Title, Abstract, Results and Discussion
1. These sections would have to be modified according to the authors’ choice for the methods:
   - either be descriptive of the cost-evolution (with lowering of objective as previously mentioned)
   - either with keeping the current objective and philosophy, but then with need of new analysis and comparison group with reference for cost-evolution.

IV. Statistical methods
1. Statistics can be improved. Only median value are presented despite the very wide SD indicate that distributions are very unlikely to be normal. There is not presentation of median, interquartile range, and extreme values, that would be of great interest

2. I agree with authors that before/after data are not independent, which is the reason why they used specific tests. However, at least for costs, it would have been possible to estimate a cost-increase per patient. If normal, this cost-increase per patient can be tested to 0 with no problem of independency (only one value left per patient: the increase). This can be also useful for a potential comparison with a reference group as suggested. This is not before/after comparisons that would be performed but cost-increase comparisons, with independent variables for mean cost-increase in the compared groups.

V. Discussion
The consequences of the eligibility criteria on the population studied are not discussed:
They imply that nor SRI short-users, nor switchers from SRIs to benzodiazepines, while benzodiazepine new initiators included can have later switched to SRI (after a treatment period >90d). Indeed, for the last three months of post index period, the patients can be no more users of benzodiazepine but to SRI and the accident-related to benzodiazepine less likely to be related to their previous use, unless a comparison demonstrates that there in an excess risk in patients who had benzodiazepines compared to others.

As these are really major comments that would lead to completely revise the manuscript, I don’t add comments for minor revisions.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, and I have assessed the statistics in my report.

**Declaration of competing interests:**

No conflict of interest for the study reviewed