Author's response to reviews

Title: Change in healthcare utilization and costs following initiation of benzodiazepine therapy for long-term treatment of generalized anxiety disorder: A retrospective cohort study

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Author's response to reviews: see over
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Ms. Deesha Majithia  
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Dear Ms. Majithia:

My colleagues and I wish to thank you for your interest in our manuscript (MS 201643846659140, "Clinical and Economic Consequences of Long-Term Use of Benzodiazepines in Patients with Generalized Anxiety Disorder"). We modified our paper based on the comment we received from the reviewers, as described below.

Reviewer 1: Antoine Pariente

1. 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, the design they chose do not allow determining whether the increase is related to: (1) some side-costs induced by benzodiazepine adverse effects; (2) the consideration of a new disease in patients 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; (3) 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.

We agree with the reviewer that our title is misleading and have changed it. We also agree that our study design was not perfect for studying the reasons for change in costs after initiation of benzodiazepine therapy for GAD, but we believe that no observational study design for this purpose is without flaws. We described changes in healthcare utilization and costs after initiation of long-term benzodiazepine therapy and focused on all healthcare encounters (and their corresponding costs) that are associated with well-known sequelae of long-term benzodiazepine use (i.e., “accident-related” care and “other possibly related care” [e.g., drug dependence/addiction/poisoning/withdrawal, drowsiness, ataxia, diplopia, vertigo/dizziness, mental confusion/disorientation, cognitive impairment]); all other healthcare encounters and associated costs were designated as unrelated to benzodiazepine use. We have changed the description of our study objective, limiting it to an examination of “the changes in healthcare utilization and costs” following long-term benzodiazepine initiation in GAD patients. While our finding
that almost 50% of the cost increase was due to sequela of long-term benzodiazepine use cannot be definitively linked to the initiation of benzodiazepines, we believe that it is certainly noteworthy and, at a minimum, hypothesis generating.

As the reviewer has pointed out, there are several explanations for increased costs in the post period that we did not mention in our original discussion. We now commence our discussion with the most important of these, namely that initiation of a new therapy may be a marker of disease exacerbation. We have not, however, followed the reviewer’s suggestion as to undertaking a comparison of the evolution of costs in patients commencing SSRI therapy for GAD. On the one hand we believe that such a comparison might be helpful in understanding the impact of initiation of benzodiazepine therapy on costs of care for GAD, since both groups would be similar in that they were initiating a new therapy. On the other hand, we are concerned about the possibility of confounding by disease severity, and possibly other factors that also are not measurable in healthcare claims databases. For example, are patients who initiate a course of therapy with selective serotonin reuptake inhibitors (SSRI) (either as monotherapy or as adjunctive therapy) similar in terms of disease severity (and other unmeasurable potential confounders) to those who initiate a course of therapy with a benzodiazepine? Without means to measure and adjust for these potential confounders, there would be no way to determine if observed differences are attributable to choice of treatment (i.e., benzodiazepine vs SSRI) or differences in underlying disease severity/other unmeasurable factors (i.e., confounding).

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

Unfortunately, we do not have the resources to procure an updated database. We note, however, that the data are still relatively recent (i.e., the database runs through some of 2008). No further action has been taken on this comment.

3. 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.

As noted above in our response to comment #1, we have modified our paper to reflect the fact that we examined “changes in healthcare utilization and costs” (i.e., the evolution of costs) following initiation of long-term benzodiazepine therapy in GAD patients. No further action has been taken on this comment.

4. 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.

We have amended the text of our manuscript and abstract, as requested (see “Methods: Study Sample”)

5. These sections (Title, Abstract, Results, and Discussion) would have to be modified according to the authors’ choice for the methods: (i) either be descriptive of the cost-evolution (with lowering of objective as previously mentioned); or (2) either with keeping the current objective and philosophy, but then with need of new analysis and comparison group with reference for cost-evolution.

As noted above in our responses to comment #1 and comment #3, we have modified our paper to more accurately reflect our “cost evolution” approach.
6. 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.

We have added median (IQR) values for healthcare costs, as requested (see Results and Table 3).

7. 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.

As we have not modified the objective of our paper (we instead opted to revise the text to more accurately reflect our objective), we have retained the analytic methods used. Accordingly, no further action has been taken on this comment.

8. 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 is an excess risk in patients who had benzodiazepines compared to others.

In fact, all patients in our sample received a minimum of 90 days of such therapy: most received considerably more. Moreover, our study design (i.e., selecting the date of initiation of benzodiazepines as the “index date” and comparing costs during the 6-month periods before and after this date, respectively) explicitly compares the experience of patients before versus after beginning therapy with benzodiazepines. However, the reviewer is correct in stating that the benzodiazepine-related events cannot be directly related to benzodiazepine use, since we only have information concerning prescriptions received, as opposed to records of actual day-to-day use of benzodiazepines by study patients. While comparisons between our study population and a cohort commencing therapy with SSRIs (the approach suggested by the reviewer) might have increased our ability to explain changes in benzodiazepine-related costs, such an approach can easily be confounded by differences in disease severity (see our response to comment #1). No further action has been taken on this comment.

Reviewer 2: Clement Francois

1. Methods – Study sample. It is not clear why a 6 months period was chosen, and not one year has done by the same authors in a related paper (Healthcare utilization and costs in patients beginning pharmacotherapy for generalized anxiety disorder: a retrospective cohort study. Berger A, Edelsberg J, Bollu V, Alvir JM, Dugar A, Joshi AV, Oster G. BMC Psychiatry. 2011 Dec 12;11:193.) or other studies in GAD and database (Anxiety disorders, major depressive disorder and the dynamic relationship between these conditions: treatment patterns and cost analysis. Francois C, Despiegel N, Maman K, Saragoussi D, Auquier P. J Med Econ. 2010 Mar;13(1):99-109). This would make comparison with these other papers in GAD easier.

We chose a 6-month period so that the link between ≥90 days of benzodiazepine therapy and the benzodiazepine-related sequelae of interest would be stronger. Comparisons with other papers concerning the costs of GAD would not be especially relevant since the objective of our current paper is not to examine patterns of utilization and cost of healthcare services for the treatment of GAD, but rather to document changes in costs of care for various events (e.g., falls, accidents) associated with long-term use of benzodiazepine therapy among patients experiencing an episode of GAD. We have added mention or two of our prior studies to the discussion section, but only in support of our finding of a non-specific cost increase after initiation of pharmacotherapy (either first-line or add-on therapy) for GAD.
2. Discussion. The increase is pre and post is something observed in GAD studies (Berger 2011, Francois 2010) who reported increase between $4812 during pretreatment to $7812. However in this case the index case is if I read correctly the prescription of benzodiazepine, so the episode of GAD could have started before. It would be interesting to see how the prescription of benzodiazepine contributes to the increase of the post treatment phase of GAD.

We agree that this is an interesting question that is worthy of study. We note, however, that answering this question would require a different study design than the one that we employed. As noted in our response to comment #1 from this reviewer, our study was designed to examine the changes in healthcare utilization and costs after initiation of long-term benzodiazepine use among patients with GAD and undoubtedly included patients with recent onset of GAD as well as those with longstanding disease. We note that our database contains a minimum of clinical information, so that we only can ascertain when GAD was first diagnosed as opposed to when this disorder actually first manifested itself. Thus it would be difficult to ascertain the true costs of GAD prior to the initiation of benzodiazepine therapy.

3. A higher proportion of patients had co morbid depression compared to the other author’s study in GAD (45.3 vs 37.8%). Authors should discuss how the high proportion of co morbid depression may have influenced the results.

The proportion of patients with comorbid depression in this study was only modestly higher (7.5 percentage points) than that in our prior study. As the reviewer pointed out in his first comment, direct comparison between the two studies is not feasible due to the difference in study periods. Also, we do not believe that the proportion of patients with comorbid depression in the current study is so high as to make it unrepresentative of GAD patients initiating long-term benzodiazepine therapy. Therefore we have not speculated in the discussion as to how co-morbid depression may have influenced the results.

4. Also but this may be outside the scope of the analysis, but it would have been helpful to have some kind of control group of GAD on long term use of SSRI or SNRIs – this would have help to the interpretation of the results - here the increased may have been triggered by a more severe population of GAD that needs long term treatment – so a control group with some kind of propensity matching will really add value to the analysis.

As noted in our response to Reviewer #1 above (see comment #1), we agree that inclusion of a comparison group that was defined by long-term use of an agent other than a benzodiazepine might have shed light on the degree to which choice of treatment is associated with costs of care for an episode of GAD. As noted above, however, control of potential confounding would likely be relatively difficult given the limitations of the database (i.e., insuring that patients who initiate long-term treatment with benzodiazepines were at clinical equipoise vis-à-vis those who initiate such treatment with SSRI/SNRI). On the other hand, given that the purpose of our study was to examine changes in costs associated with well-known sequelae of long-term benzodiazepine use among patients with GAD, we believe that our use of each patient as his/her own “control” is sufficient. Accordingly, no further action has been taken on this comment.

Editorial Office Request

1. In addition to this please could we ask that you also address the following editorial point: Authors’ contributions – Please include an Authors’ contributions section before the Acknowledgements and Reference list.

We have added this section to our manuscript, as requested.

We thank you again for your interest in our manuscript. Please feel free to contact me if you have any additional questions or concerns. My colleagues and I look forward to hearing from you soon.
Sincerely,

Ariel Berger, M.P.H.