Author's response to reviews

Title: Aspirin and Multiple Sclerosis

Authors:

Sheila Tsau (sstsau@yahoo.com)
Mitchell R Emerson (memers@midwestern.edu)
Sharon G Lynch (SLYNCH@kumc.edu)
Steven M LeVine (slevine@kumc.edu)

Version: 2 Date: 19 May 2015

Author's response to reviews: see over
Dear Dr. D’Souza,

We thank the Reviewers and the Developmental Editor for their comments on our paper entitled “Aspirin in Multiple Sclerosis.” Our paper has been revised in accordance with their suggestions and the additional editorial requests (at the end). Please find below our responses (indented sentences) to the individual comments (changes to the text are identified by a Red font, and references are in Blue as their numbering has changed). We hope you find these changes to be satisfactory.

Sincerely,

Steven LeVine, Ph.D.

Reviewer 1: Friedemann Paul
In general, this is a well-written and comprehensive review on an interesting and important topic. I have a few suggestions for a revised paper.

Thank you.

Minor essential revisions
1. A figure could be added to illustrate the MOA of aspirin
   
   We have added Figure 1 to illustrate the MOA.

2. Introduction: "A substantial percentage...." This reads rather speculative, any concrete data on that?
   
   This statement has been removed as we are not aware of any concrete data on this topic.

3. Introduction: "Vascular changes include....." Please add ref. PMID:17382348
   
   This reference has been added to the Introduction (page 3; reference 13).

4. p6 "...their physical activity may contribute to the higher prevalence...." This is not entirely true for the MS population as a whole given that many patients are diagnosed earlier and have little or no disability so one would not expect reduced physical activity in EDSS ranges 0-1, perhaps 2. So the authors should add whether there are data on an association of vascular events with disease duration and/or EDSS and not just a diagnosis of MS
   
   This sentence has been rewritten so that it now reads “Physical inactivity, particularly in patients needing a wheelchair or who are bedridden, may contribute to the higher prevalence...” (page 4; bottom paragraph).

5. p6. "Additionally, a positive association...." It is not entirely clear what the authors mean, please describe this in more detail and comment on the robustness of the original data underlying this assumption. As the therapeutic landscape is changing rapidly the author should add if available data on newer compounds such as fingolimod (cardiac side effects!), dimethylfumarate and teriflunomide,
as there are probably no thorough analyses on this issue the authors could have a look at published side effects from the pivotal trials

We have added more details and commented on the robustness of the correlation expanding this topic to three sentences rather than one (page 5; paragraph 2; sentences 3-5). We have also added three sentences about newer compounds (page 5; paragraph 2; last three sentences).

6. p7 "Increased risk of dying from cardiovascular disease" The authors should add some more ideas what the underlying cause could be. They nicely summarize animal data on platelet activation in EAE etc., however, the association in human disease remains blurry. For example, see recent data on an association of metabolic alterations/obesity in MS as a possible link PMID:24048545, PMID:24347183, PMID:25182290, PMID:22952735.

We added a paragraph, together with the suggested references, regarding more ideas about the causes for increased risks of dying (page 6; paragraph 2; references 52-56). Note, we replaced the Wesnes et al. paper (25182290) with other references (42,52,56) since it was about the risk for getting multiple sclerosis, which is outside the scope of our paper that is focused on patients that already have multiple sclerosis.

7. p9. on vessel congestion/perfusion of cerebral structure, please add PMID: 22736752 as relevant paper in this context

This citation has been added (page 13; paragraph 3; reference 121).

8. p13. on suggested causes of fatigue: please add recent data on impaired functional connectivity associated with/ as a cause of fatigue, see PMID 24347184, PMID:25392321

We added impaired connectivity as a cause of fatigue. Reference 25392321 was added, but not 24347184, since this latter did not include fatigue in their study (page 16; last paragraph; reference 170).


These topics and references have been added (page 16; last paragraph; reference 172, 173, 175).

10. p14 on ASA studies in fatigue: risk of bleeding as side effect should be mentioned and undiagnosed sleep disorders as underlying fatigue cause should be mentioned as this may have a relevant confounder and could explain inconsistent results resp. lack of a clear effect of ASA on fatigue, see also PMID: 24360534.

Risk of bleeding is covered under the section “Potential risks associated with ASA use in MS.” (page 20; paragraphs 1-3). In particular, increased cerebral bleeding and increased gastrointestinal bleeding are discussed as these are the main sites of bleeding associated with ASA usage. The idea that an undiagnosed sleep disorder could be a confounder is intriguing and
Reviewer 2: Robert Zivadinov

Reviewer’s report:

• The paper is completely neglecting an important aspect of MS disease process, which is development of anti-phospholipid antibodies (APLA). It has been shown in numerous papers that prevalence of APLA is increasing with severity of the diseases course (see Garg, Mult Scler, 2007 and J Neuroimmunol, 2007; Bidot, BMC Neurol, 2007; Stosic, J Neurol, 2010, Horstman, J Neuroinflamm, 2009). Please provide another section linking APLA with MS, which is more relevant for ASA argument then most of the mechanisms the authors focused on.

We thank the reviewer for this comment. This is now covered in the new section on “ASA and antiphospholipid antibodies.” It has been added to page 11, paragraph 1, of this section. The suggested references have been added (97,98,100,101,103).

• APLA can be altered by ASA; many MS pts are receiving ASA for secondary APLA syndrome, and as far can be judged from the paper, this argument was not discussed. Provide section on APLA and ASA.

A section covering this item has been added (page 11; paragraphs 1 and 2 in the section “ASA and antiphospholipid antibodies”).

• APLA can be altered by DMTs (for example see Zivadinov et al, Neurol Res, 2012). Please comment on use of ASA for APLA in MS.

We added the suggested reference (reference 102, in particular, 5th sentence in 1st paragraph of the section “ASA and antiphospholipid antibodies” on page 11) and have commented on the use of ASA for APLA in MS (page 11-12; 2nd paragraph of the section “ASA and antiphospholipid antibodies”).

• There are number of sections which are not well connected. The authors should divide mechanism of action of ASA, to cardiovascular risk factors in MS to treatment related potential of ASA. As it now stands, basically the paper is mini review of everything: cardiovascular risk factors, mechanisms involved of MS damage, experimental models and treatments trials and the reader is lost with the overall message about what this paper is about. Sections are not very well flowing each after another.

We have reorganized the manuscript in line with this suggestion, and the first two major sections are organized to 1) “Cardiovascular Risks in MS” (starting on page 3) and 2) “Treatment Potential of ASA in MS Patients” (starting on page 6). We have also added sentences at the start of multiple sections to better connect the sections, which is also in line with the Developmental Editor’s suggestion.

• Studies on ASA in MS should be better organized. A Table of all trials of ASA in MS would be very helpful.

We have reorganized the sequence of the relevant sections (see above response), and changed the presentation of the contents within the section on “ASA in MS and EAE studies” to have better flow. In addition, we have added sentences to better connect the sections (see above,
and also in response to the Developmental Editors comments). Table 1 includes the trials performed in MS patients, so we did not feel justified to include an additional table that would be redundant, but we have expanded Table 1 to include those studies covered in the section “ASA in MS, EAE and related studies” and select studies related to “ASA and antiphospholipid antibodies.” Since only a very limited number of studies have been performed examining ASA effects on the disease course in MS (now covered in Table 1), and these studies are very old using outdated outcome measures, we did not think a separate table would be justified.

Minor essential revisions:

• Some sections of the paper are misleading. For instance providing subtitles like ASA and cardiovascular risk factors in MS indicates that this is the argument what authors are focusing on, when in fact is just cardiovascular risk factors and MS.

We have rephrased this subtitle so that it now just focuses on “Cardiovascular Risks in MS” (page 3). Some other subtitles also have been rephrased.

• Please add recently published study on Cardiovascular risk factors and MRI outcomes in MS (Kappus et al, JNNP, 2015).

This reference has been added (page 5; reference 45).

Developmental Editor: Hannah Robertson

Recommended structural revisions:

This strikes me as an interesting topic, and one that merits a thorough review. I did find it difficult to stay engaged with this review in its current state, largely for the same reasons the reviewers have already highlighted.

We have reorganized the sequence of sections (e.g., “Cardiovascular Risks in MS” now follows the “Introduction”), we have substantially reorganized and rephrased the contents within sections (e.g., Introduction; Cardiovascular Risks in MS; ASA in MS, EAE and Related Studies), added or revised sentences at the start or end of sections to improve the flow or enhance clarity.

I agree that a figure on ASA mechanism of action would be useful, and a section on APL should be added. I leave it to the authors to decide where to insert the new material; I'm not sure whether it would be considered a pathology or not.

These items have been added, i.e., Figure 1 and the section “ASA and antiphospholipid antibodies.” The latter has been added immediately following the section on “Considerations regarding ASA use for cardiovascular disease in MS patients”

I would suggest summarizing the various studies described much more succinctly, with careful attention to exactly what readers really need to know about these studies to understand the potential risks and benefits of ASA treatment. For example, rather than describing the individual findings of the various studies on MS and cardiovascular disease it may be better to say something like 'There have been a number of studies examining the rate of cardiovascular disease in MS patients compared to the general population [citations here] however, the results have varied...' and go on to state
whether, on the balance, you can say whether there is an increased risk of any given type of disease, how big that increase is, and whether all studies made the same finding, but again being succinct. So, for example, ‘Taken together, these studies indicate MS patients are at increased risk of... ASA is known to reduce this risk in...’ or similar. This should help to compress each section into the most important points, and to build in some of the linking needed, as indicated by reviewer 2. A similar approach can be applied to all sections.

In prior reviews, we were criticized for presenting summaries in place of providing details of key studies. Thus, we purposely presented enough descriptions so that the reader is able to evaluate the findings from the relevant studies (please note, Reviewer 1 remarked as a positive that the review was comprehensive). However, as stated above, we have rephrased or reorganized sections (including the one identified in the above comment) in order to make the paper flow better, and in some cases to be more succinct (e.g., Introduction). We have presented two tables and one figure that summarize the contents; thus, readers who are only interested in a summary of the main points can focus on these items.

I’m not sure whether risk of cardiovascular disease, and risk of mortality from cardiovascular disease need to be two separate sections. If they can be reduced, as suggested, I think they could and probably should be rolled into one section. The linking sentence suggested (see the comments inserted directly into the manuscript) would still be important.

A linking sentence has been added as suggested. Since Reviewer 1 indicated “the authors should add some more ideas what the underlying cause could be...” to the mortality section we kept it as a separate section and expanded its contents as suggested by Reviewer 1 (page 6, paragraph 2).

I’m not sure it makes sense to talk about features of MS and the relevant properties/effects of ASA under separate headings – it ought to be possible to synthesize these into the same section. If this can’t be done, or would take too long to be worthwhile, linking will be important to keep the flow going.

We have combined all five sections under “Potential risks associated with ASA use in MS” (starting on page 19) into one section as suggested.

Although a small addition, I think it is important to state outright that it is not clear what the risk/benefit equation is for ASA in MS, and that this is going to require careful consideration. The way this review currently flows, the reader feels a bit cheated at the end to realize it’s not at all clear whether ASA is a good idea in this context.

This statement has been added to the Introduction as suggested (page 3; second to last sentence of the last paragraph of the Introduction).

Additional minor structural suggestions:
I would suggest reversing the order of the introduction so that MS comes first and ASA second.

The sequence in the Introduction has been reversed as recommended (page 3).
In the introduction I think it worth stating outright that ASA is well-known for its many effects other than analgesia – avoiding that sounds a bit coy. I know it’s hard to think of an original way to put it now, but it’s still odd not to say it.

This has been added (page 3; paragraph 2; 1st sentence).

I have inserted some comments into the manuscript with suggested ways of linking some of the sections better. Similar linking should be applied throughout, and these are just examples to show how this might be done. I have also made a few copyediting corrections/suggestions in comments and tracked changes to guide the copyediting phase.

These changes have been made as suggested.

Copyediting issues to keep in mind:

Journal style is to spell out e.g., i.e., and similar abbreviations.

These changes have been made.

Suggest ‘a unique quality’ rather than ‘a uniqueness’ for grammar.

This change has been made (page 7; paragraph 2; 1st sentence).

‘et al.’ should be ‘et al.’.

These changes have been made.

No issue number in references, as indicated in tracked changes on the first reference.

These changes have been made.

There is some unusual phrasing and usage – might be worth trying to make the language a bit more conventional.

We have tried to make the language more conventional.

Additional Editorial comments
Abstract: This should not exceed 175 words

The abstract has been reduced to 175 words.

Include an abbreviation section

An abbreviation section has been added (page 22).
Provide a statement in the author contribution that all authors read and approved the final manuscript based on the following guidelines: Authors' contributions - Please include an Authors' contributions section before the Acknowledgements and Reference list.

The requested statement has been added and author contributions have been listed prior to the Acknowledgement sections (page 23).