Author’s response to reviews

Title: Fatigue in Traumatic Brain Injury adults: predictors and consequences: a systematic review of longitudinal study protocols

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Author’s response to reviews: see over
June 20, 2013

Dear Editor:

I wish to express on behalf of our team, our sincere appreciation for the feedback received by the reviewers. We have addressed your most recent concerns and our revisions are indicated below under each comment. Enclosed please find a revised version of the paper.

We look forward to hearing from you.

Sincerely,

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Reviewer Comments and Responses:

1. You have changed the title to? Fatigue in Traumatic Brain Injury adults: predictors and consequences: a systematic review of longitudinal study protocols?, would it not make more sense to change it to Fatigue in adults with traumatic brain injury......?

Response: We agree with the reviewer and the title now is “Fatigue in adults with traumatic brain injury: predictors and consequences. A systematic review of longitudinal study protocols.”

2. Comment from reviewer: Highlight comment SJN 5/10/2013 9:16:52 AM What about studies that consider fatigue as a secondary outcome? They could still contain relevant information Authors response: We decided to consider studies that focus on fatigue as the primary outcome only. This is partially because they are expected to be more rigorous, and of better quality given the predefined hypothesis. In addition post-host analyses are not always accurate, and could potentially mislead readers.

Editor: This is not strictly true, as RCTs may have this as a secondary outcome which would not be posthoc.

Response: We agree with the editor regarding the RCTs. We decided to consider only studies that focused on fatigue as a primary outcome. RCTs data will be included for one research question (e.g. on the course
of fatigue) - see also our answer to your comment #5. This makes our statement about posthoc analyses irrelevant.

3. Comment from reviewer: Highlight comment SJN 5/10/2013 9:22:43 AM Why exclude these types of study? Exclusion of unpublished data could lead to publication bias Authors response: We updated our exclusion criteria:
Editor: This does not make sense as conference abstracts and unpublished studies are still in the exclusion criteria. You need to be consistent, also with the final line in the discussion.
Response: We thank reviewer for this comment. We have discussed this and agreed to exclude conference abstracts, theses, and unpublished manuscripts. Royle et al. have shown in systematic reviews in the field of diabetes that: 1) by searching the Conference Proceedings Index/ BIOSIS / Science Citation Index only few are published as journal articles (e.g. none/12%/30%) – and that we are unlikely to access the information necessary to perform a quality assessment; 2) 92% of the dissertations appeared to have been written up as articles in journals indexed in MEDLINE/ EMBASE. Therefore, our search will capture those; 3) unpublished manuscripts, or the grey literatures are often lacking in detail, and consequently are difficult to appraise scientifically.


4. Comment from reviewer: Highlight comment SJN 5/10/2013 9:54:13 AM Could pharmacological interventions in this area have side effects of fatigue, therefore confounding the disease process of fatigue following TBI?
Authors response: We will undertake a detailed review of the medications when the data is available. We will focus on the commonly used medications in the TBI population (e.g. antiepileptics, antipsychotics, antihistamines, corticosteroids, antidepressants, etc.) that can cause fatigue.
Editor: would it make more sense to include this in your protocol?
Response: Agreed. The following paragraph has been added to the text (page 5, first paragraph):
A detailed review of the medications (whenever available) will be undertaken and reported, as many of them, including those commonly used on the TBI population (e.g. antiepileptics, antipsychotics, antihistamines, corticosteroids, antidepressants, etc.), can cause fatigue.
We updated the tables accordingly.

5. You have stated you will only use the control arm of an RCT for objective 2, but your methods do not specify how you will meet each objective."
Response: The following has been added to the Data extraction section:
The observational studies data will be used to address all three research objectives. The RCTs data will be used to answer the research question on the course of fatigue in TBI only. The following steps will be taken while working with the RCT data: 1) identification of RCTs with a focus on fatigue as primary outcome; 2) identification of treatment arms (e.g. intervention/ no intervention); 4) the course of fatigue in untreated (e.g. no intervention) arm will be reported; 5) in groups where treatment did not produce an effect, the course of fatigue will be reported in both arms.
The following has been added to the Data synthesis:
We will divide the results of each study into three main categories: course of the fatigue, prognostic factors and consequences of fatigue. To determine the course of fatigue per study an overall percentage of fatigue as primary outcome measure will be reported. Fatigue resolution/exacerbation/no change will be identified and reported as: “less fatigue”, “more fatigue”, “no fatigue”, etc. Next, a range and median (using the overall percentages) will be calculated for the number of studies reporting on the outcome measure. Prognostic factors associated with fatigue will be extracted from all cohorts (and untreated/without an effect RCTs). All factors influencing the course of fatigue as reported by the author will be considered to be prognostic factors. We will consider a prognostic association as significant if 1) the reported \( p \)-value is less than 0.05; 2) the author reported that an association was significant; 3) the 95% confidence intervals around a rate ratio or similar statistic did not include 1. Where a prognostic factor was assessed with respect to the outcome at a number of time-points in one cohort, data will be extracted and reported for each follow-up. To address our third research objective (e.g. health consequences of fatigue in TBI) we will evaluate the literature regarding putative negative effects (e.g. quality of life, morbidity, mortality, costs, satisfaction, etc.) associated with fatigue after TBI at each point of time. The instrument that was used (e.g. single item, standardized/non-standardized, and validated/non-validated) for reporting will be defined and specified. Understanding that establishing the causal links between fatigue and health outcomes may be difficult in TBI, we will use the following criteria in our report: temporal relationship, lack of alternative causes, outcome response to alleviation/exacerbation of fatigue over time, etc. Confounding factors (such as sociodemographic characteristics, severity of injury, co-morbidities, etc.) which may affect the generalizability of the study and interpretation of results will be explored and clearly described. In addition, we will report on the possible effects of individual study quality indicators (e.g. follow up period and instrument used to measure outcome), on study design and study size [12].